

Demystifying Medicine Tuberculosis: Return of the “White Plague”

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February 3, 2015

Case Scenario 1

49 year old male presents with cough x5 months that has gradually gotten worse. Patient's cough is productive of yellow phlegm and has persisted despite OTC cough remedies. His phlegm has occasionally been blood-tinged recently. He does not have a stuffy or runny nose or sore throat. He also reports subjective intermittent fevers and feeling poorly. He has some sweats at night when he sleeps but attributes this to not having air conditioning in the homeless shelter where he stays. He has lost weight but says this is due to not having consistent meals. He does not feel short of breath and has been able to continue working during the day selling newspapers. He has otherwise been relatively healthy and does not take any regular medicines. He smokes 1 ppd for 10 years but does not drink or do drugs. No one else around him has been sick, that he knows of.

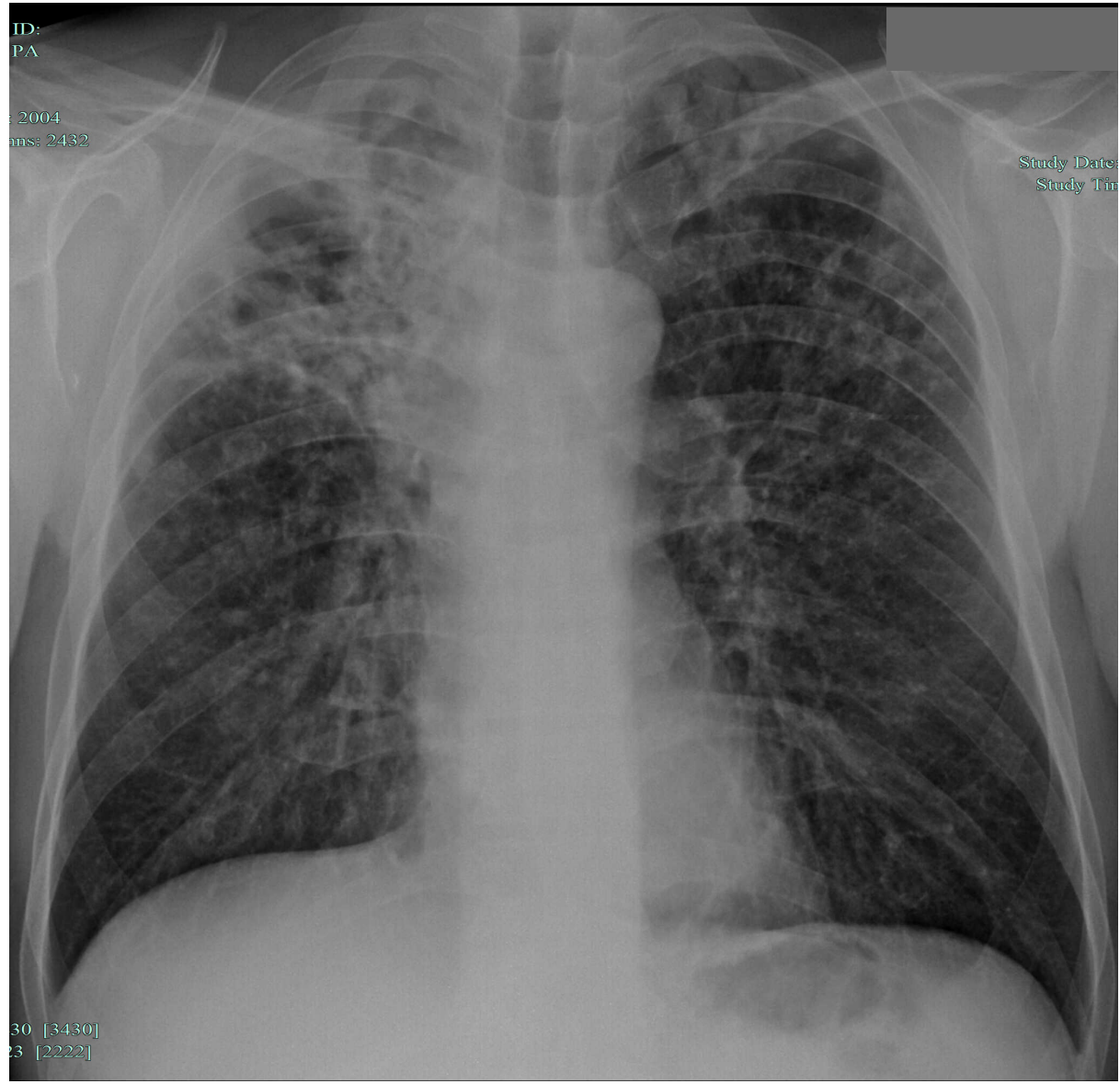
Case Scenario 1

PE: thin W/M in
no distress

Temp: 99.6 °F;
BP 135/72; HR
96; RR 20

Physical exam is
normal,
including the
lung exam.

CXR:



Case Scenario 1

He does not look too sick and chronic coughs are common, especially in smokers. What do you do next?

- A. This is probably a smoker's cough. Give him Robitussin and have him follow-up in 1-2 weeks if not better.
- B. This probably started as the common cold that has since developed into a bacterial infection. Give him a Z-pack to cover the most common bacterial causes and have him follow-up in 1-2 weeks if not better.
- C. This is concerning for active TB. Send a sputum sample to the lab to look for TB. Since he does not appear to be too sick, start empiric TB therapy as an outpatient and have him follow-up in 1 week.
- D. This is concerning for active TB. Admit him to the hospital for evaluation and empiric TB therapy.

Case Scenario 2

25 year old Asian female immigrated to the US at age 3 with her family. She just started her graduate degree program in microbiology and had a routine PPD placed on her arm due to her area of research. It comes back positive at 22 mm and she is referred to you for evaluation. She had never had a PPD test done before. She reports being otherwise healthy and is on no medications except for birth control pills. She reports receiving a BCG vaccination as an infant and attributes the positive PPD to that. She has a normal physical exam and her CXR is also normal.

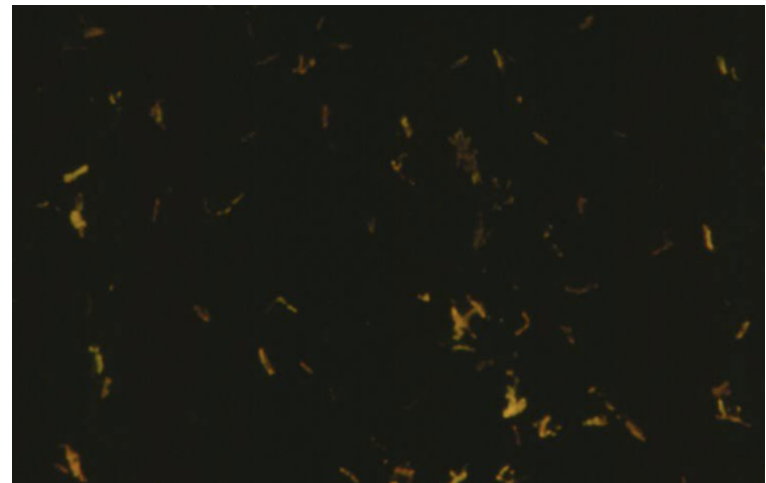
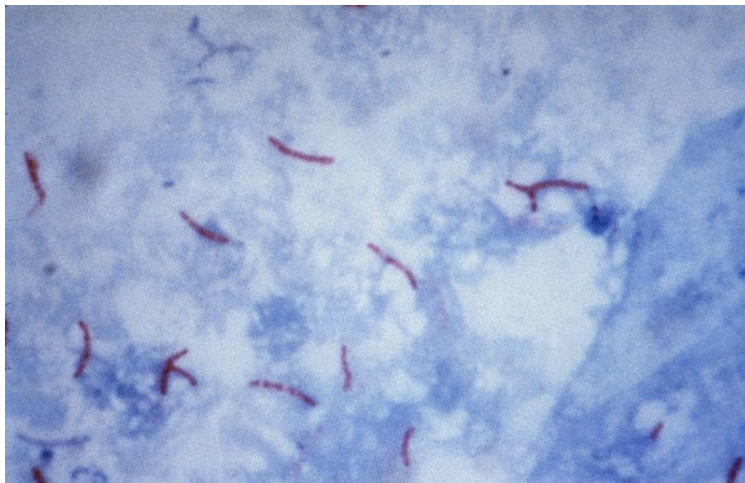
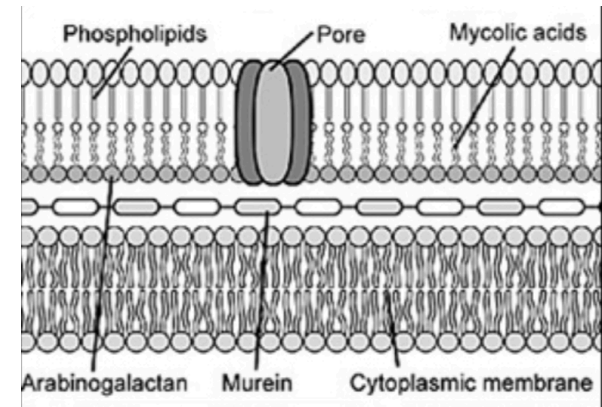
Case Scenario 2

What do you recommend?

- A. Her positive PPD is likely due to her previous BCG vaccination and will always be positive. Nothing further needs to be done.
- B. She has latent TB infection. Recommend treatment with isoniazid daily for 9 months.
- C. She has latent TB infection. Recommend treatment with rifampin daily for 4 months.
- D. She has latent TB infection. Recommend treatment with isoniazid/rifapentine once weekly for 12 weeks.

What is TB?

- Small aerobic bacillus with high lipid content in cell wall; retains certain stains even after acidic wash, thus “acid-fast”
 - Ziehl-Neelsen stain
 - Auramine-rhodamine stain with fluorescence microscopy

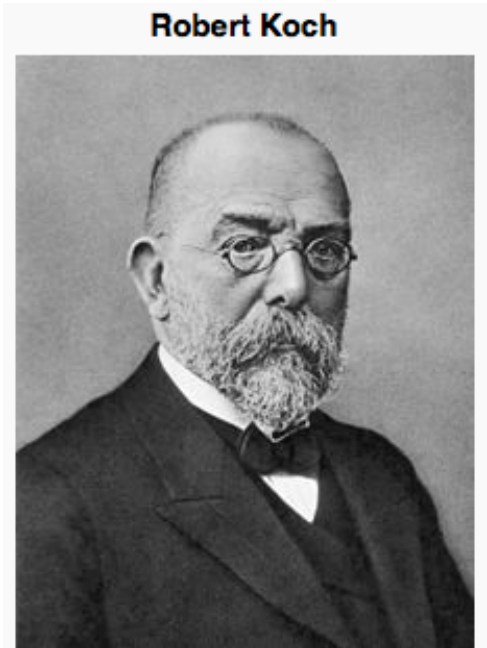


History of TB

- TB has been around for thousands of years and known as consumption, wasting disease, white plague
- Believed to be hereditary until 1865, when Jean-Antoine Villemin demonstrated TB infectious by transmitting from humans to rabbits, cattle to rabbits, and rabbits to rabbits
- In 1882, Robert Koch identified the *Mycobacterium tuberculosis* bacterium; won 1905 Nobel Prize in Physiology and Medicine for his work



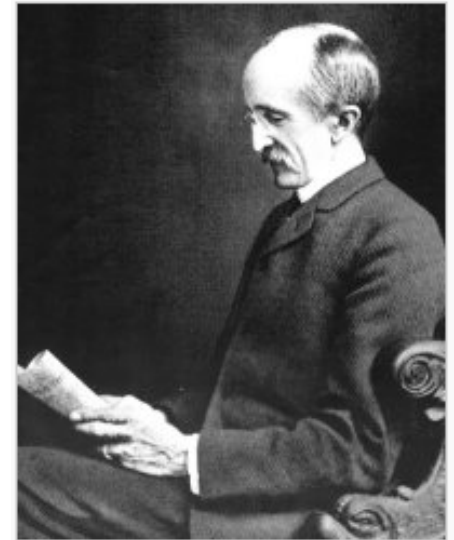
Jean-Antoine Villemin



Robert Koch

History of TB

- Before 1940s, no treatment available
- Patients sent to sanatoria for “treatment” with bed rest, good nutrition, fresh air, sunshine
- Edward Livingstone Trudeau (1848-1915) opened first sanitarium in US
 - When 19, watched older brother die of TB
 - 1 year after med school, contracted TB; went to favorite resort in Adirondacks to die but instead slowly regained strength
 - Believed improvement due to healthy diet, outdoor exercise; belief confirmed by experiments in tubercular rabbits
 - Established Adirondack Cottage Sanitarium in 1885



Dr. Edward Trudeau

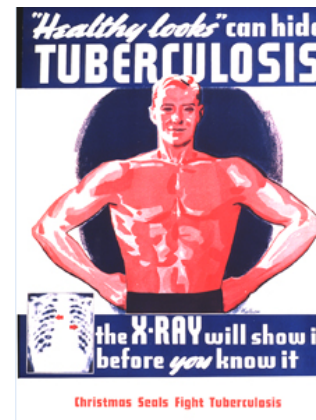
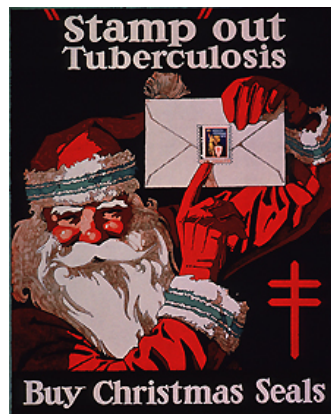
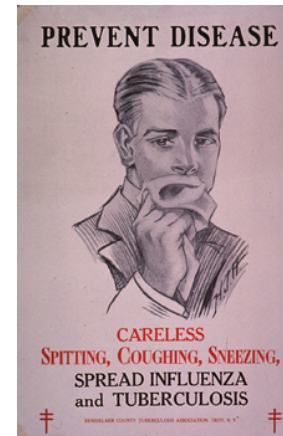
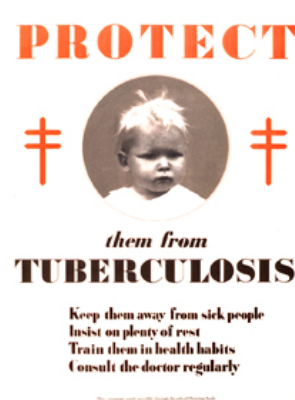
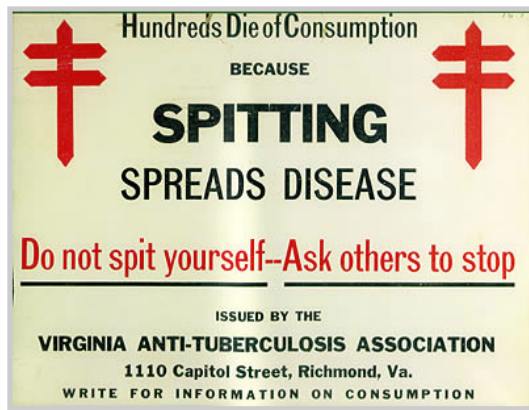


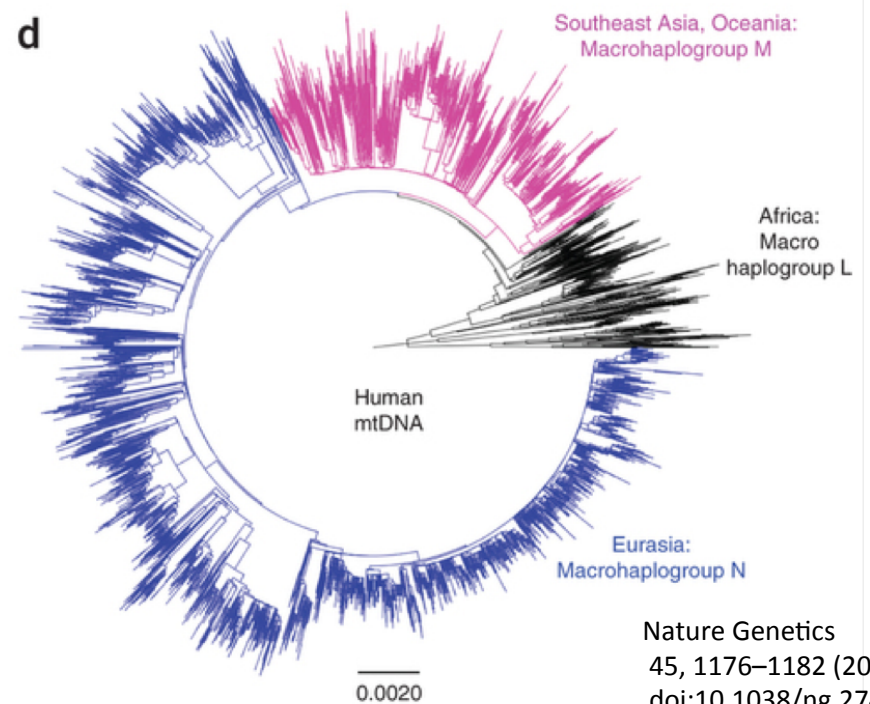
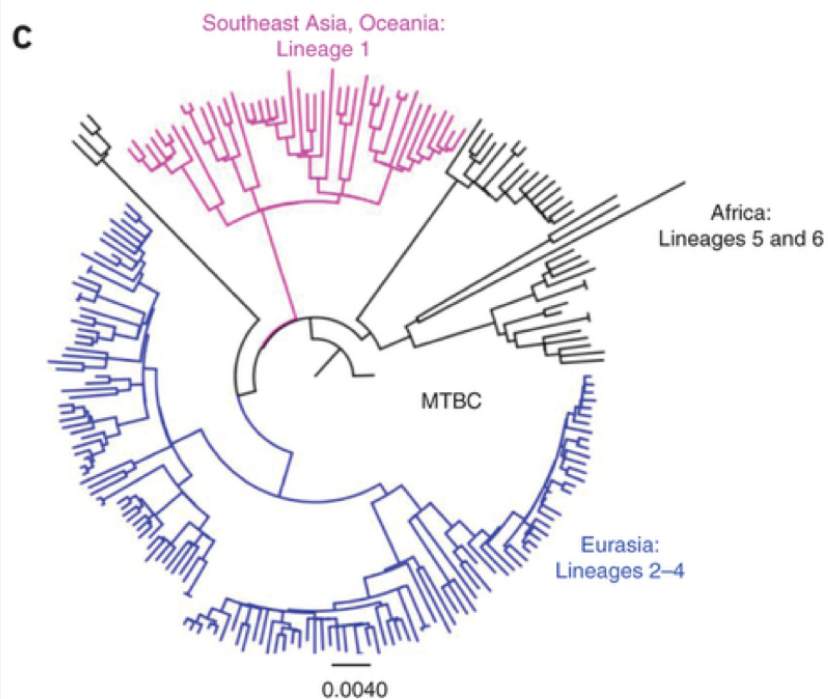
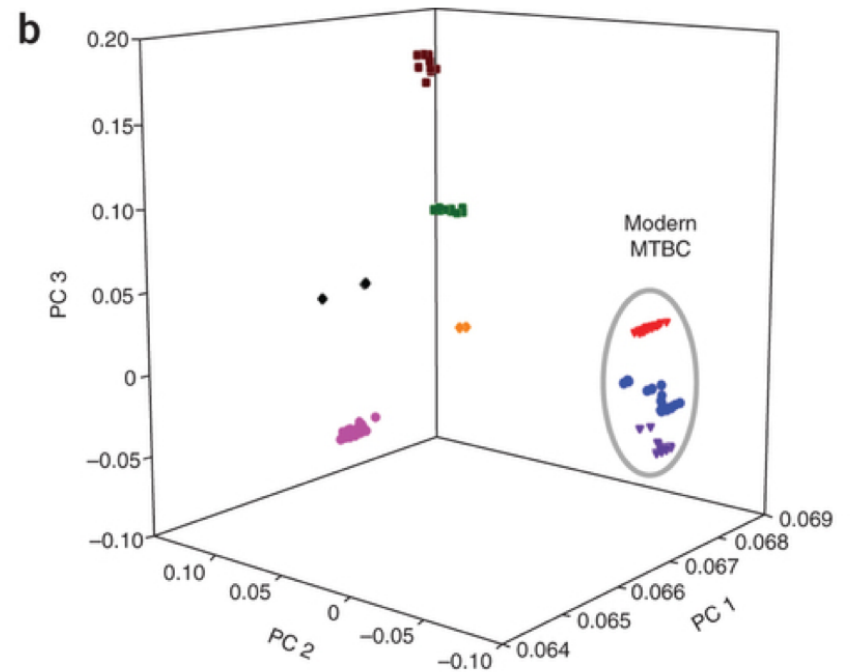
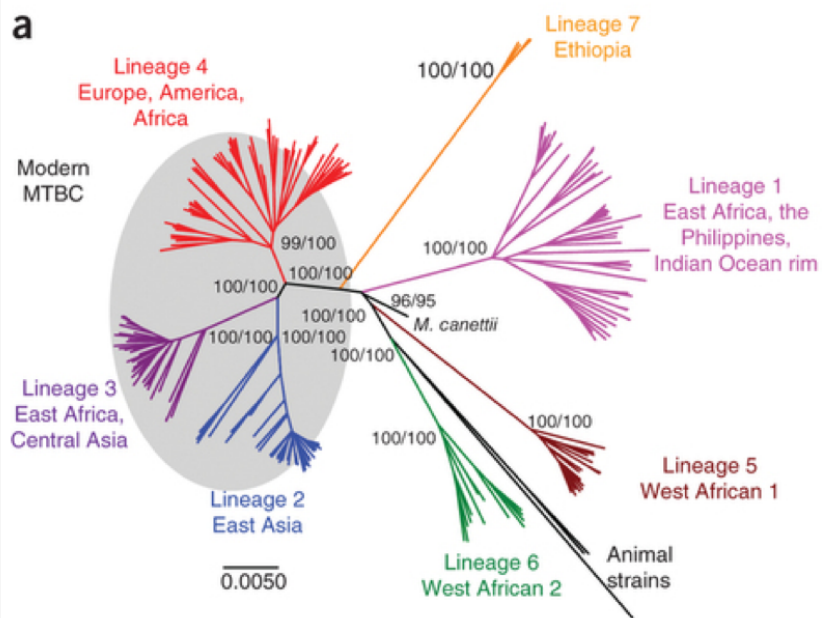
1906 view of the Chapel and cure cottages shown above

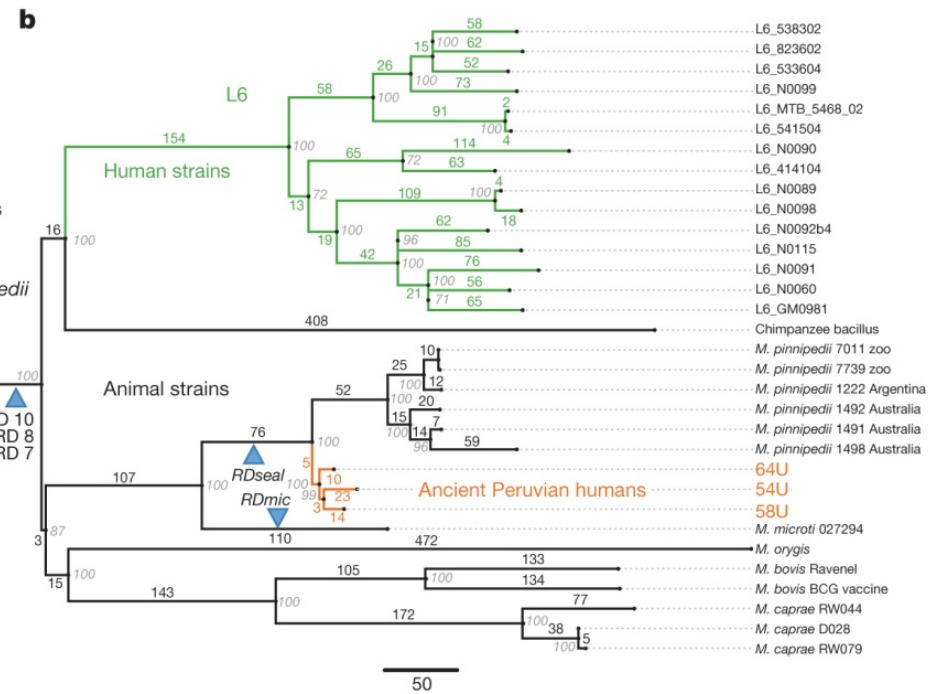
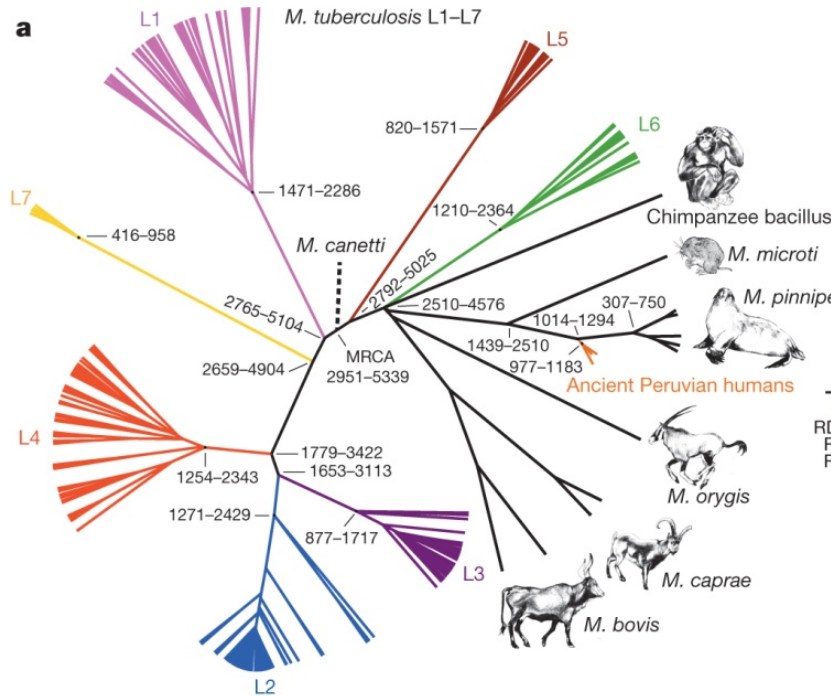


History of TB

- Public health campaigns by the Red Cross and the American Lung Association

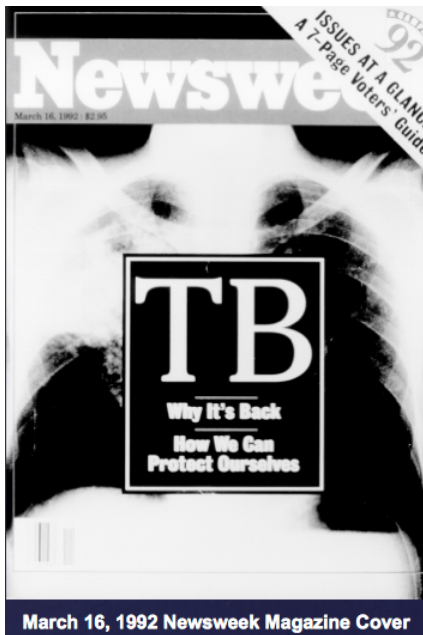






TB Treatment

- Anti-TB drugs discovered beginning in 1940s
 - 1943: streptomycin
 - 1943-1952: isoniazid, p-aminosalicylic acid (PAS)
- Sanatoria became obsolete and most closed by 1970s
- But TB resurgence in 1980s due to complacency, reduced funding, increased immigration, HIV epidemic, spread of MDR-TB



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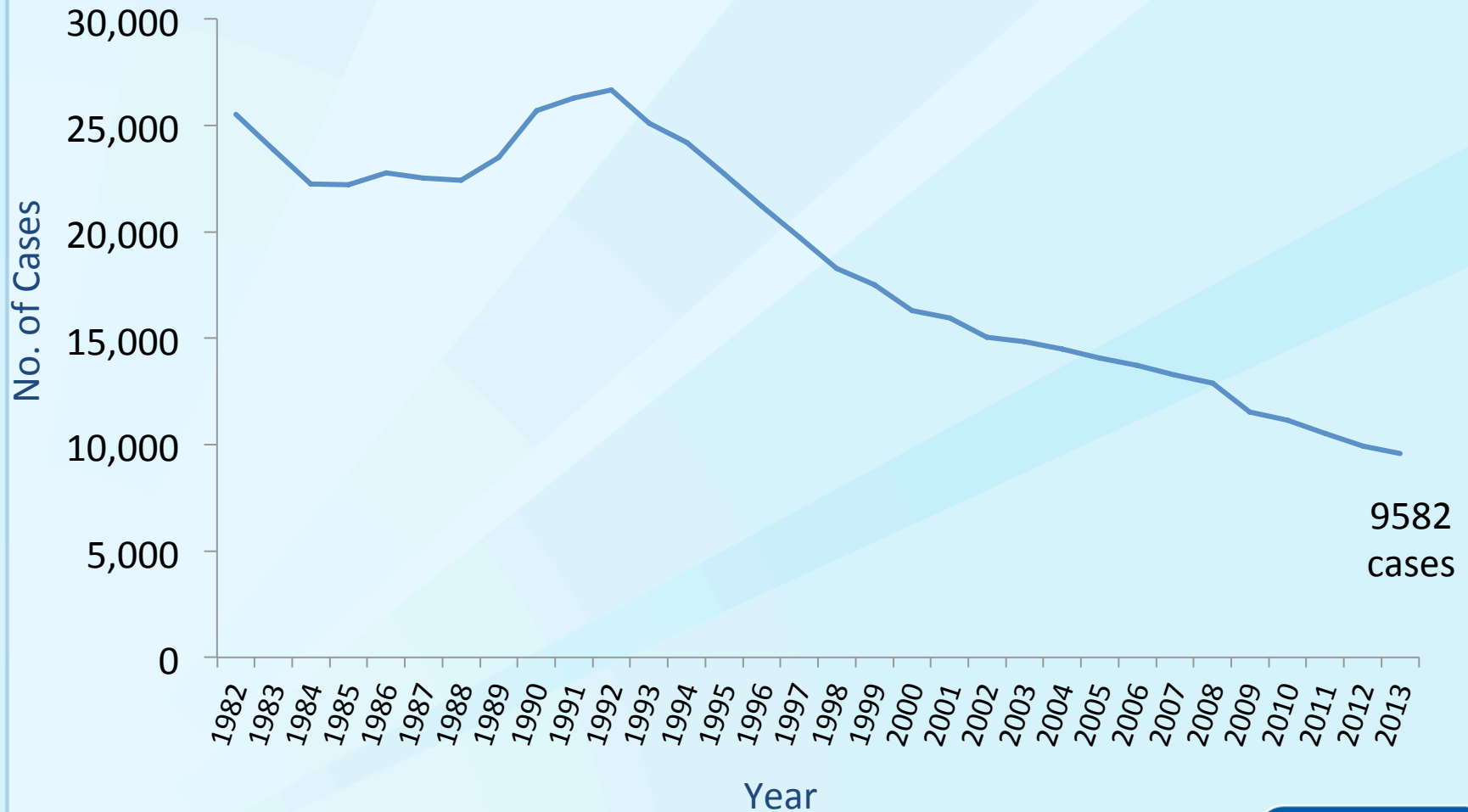
FEBRUARY 25, 1993

Number 8

THE EMERGENCE OF DRUG-RESISTANT TUBERCULOSIS IN NEW YORK CITY

THOMAS R. FRIEDEN, M.D., M.P.H., TIMOTHY STERLING, M.D., ARIEL PABLOS-MENDEZ, M.D., M.P.H.,
JAMES O. KILBURN, PH.D., GEORGE M. CAUTHEN, Sc.D., AND SAMUEL W. DOOLEY, M.D.

Reported TB Cases United States, 1982–2013*



*Updated as of June 11, 2014.



TB Morbidity

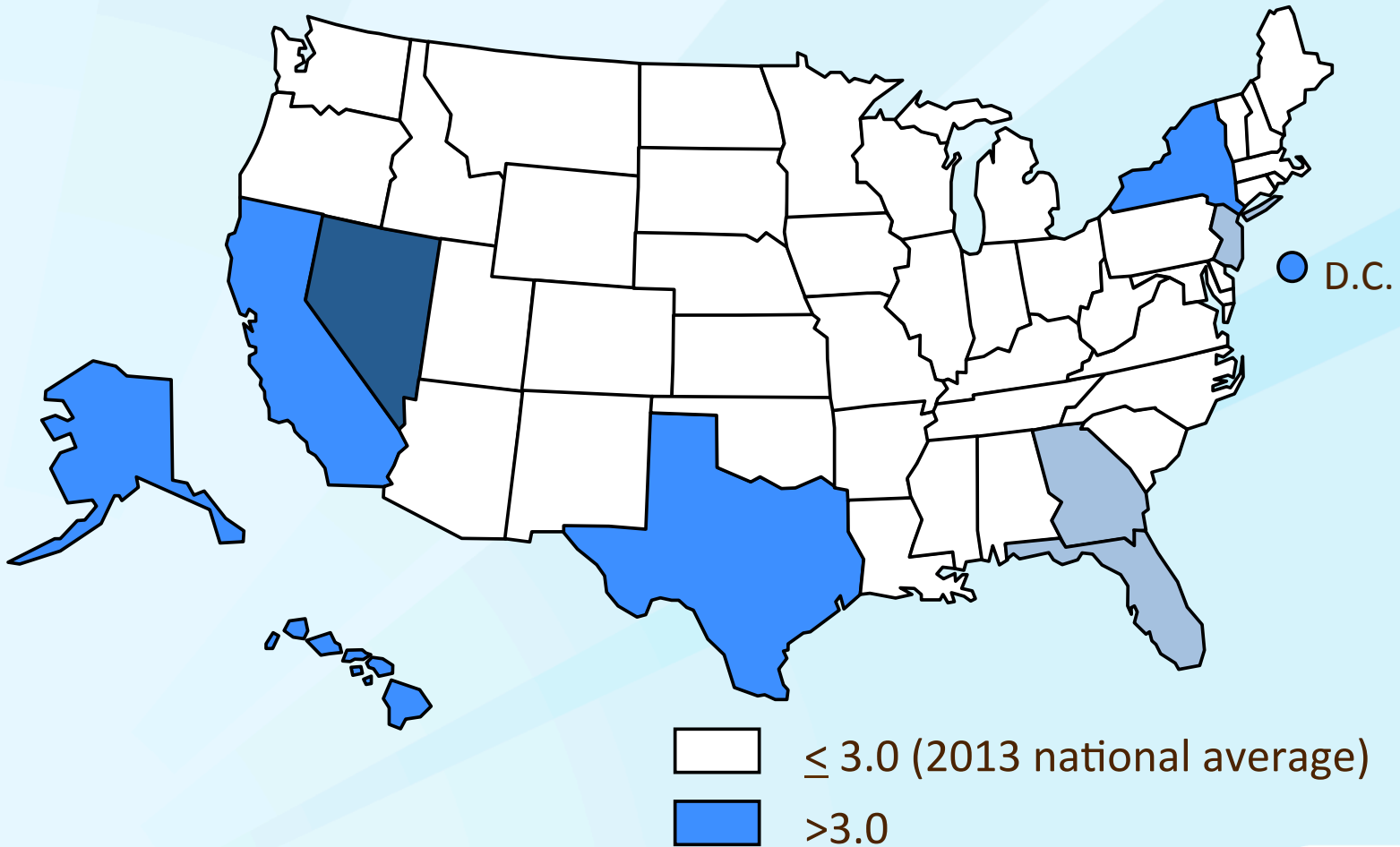
United States, 2008–2013

Year	No.	Rate*		
2008	12,893	4.2		
2009	11,519	3.8		
2010	11,164	3.6	Canada	5
2011	10,509	3.4	UK	13
2012	9,940	3.2	China	70
2013	9,582	3.0	Russia	89
			S. Korea	97
			India	171
			S. Africa	860
			Swaziland	1380

*Cases per 100,000. Updated as of June 11, 2014.



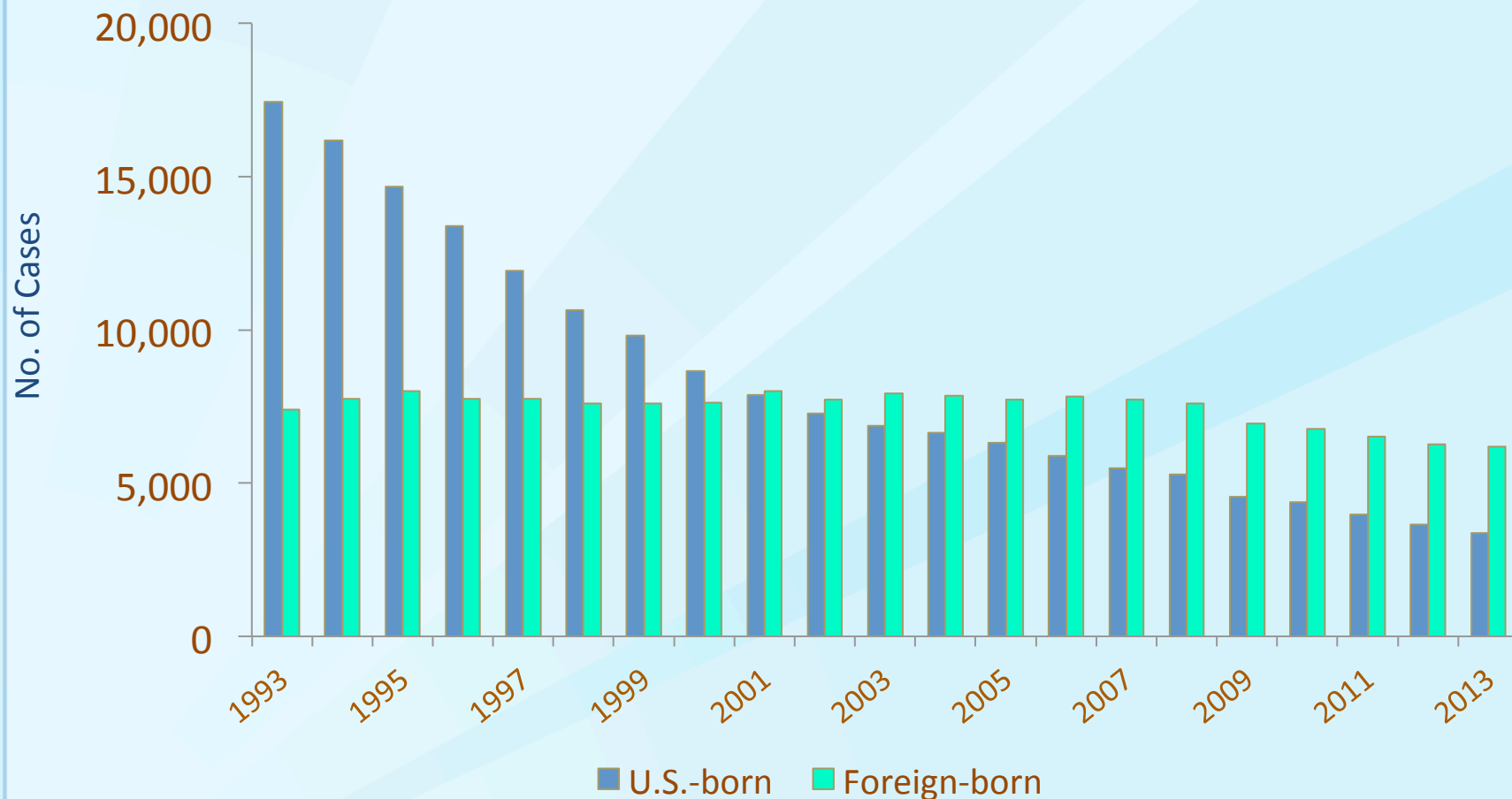
TB Case Rates,* United States, 2013



*Cases per 100,000.



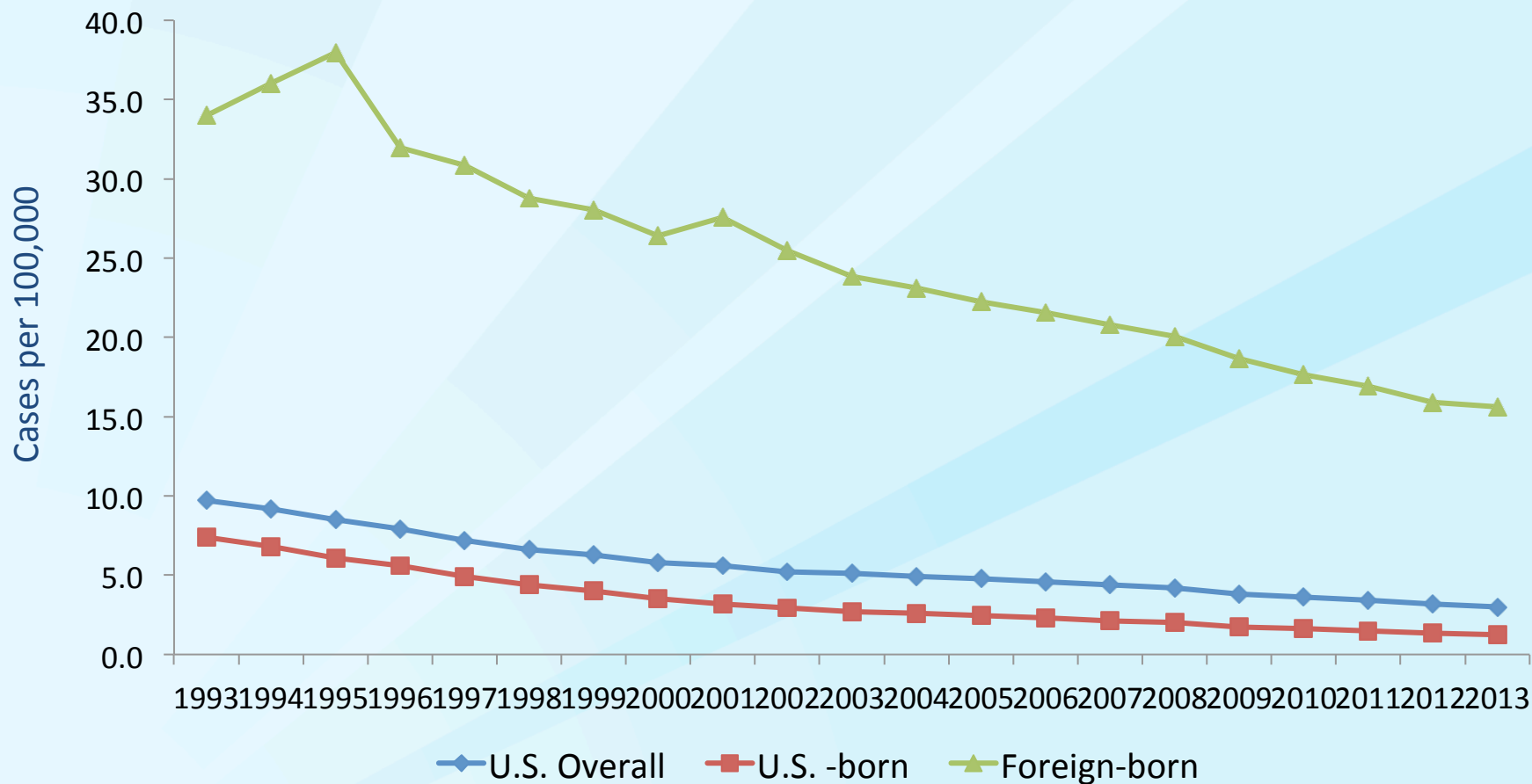
Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2013*



*Updated as of June 11, 2014.



TB Case Rates in U.S.-born vs. Foreign-born Persons, United States, 1993 – 2013*



*Updated as of June 11, 2014.



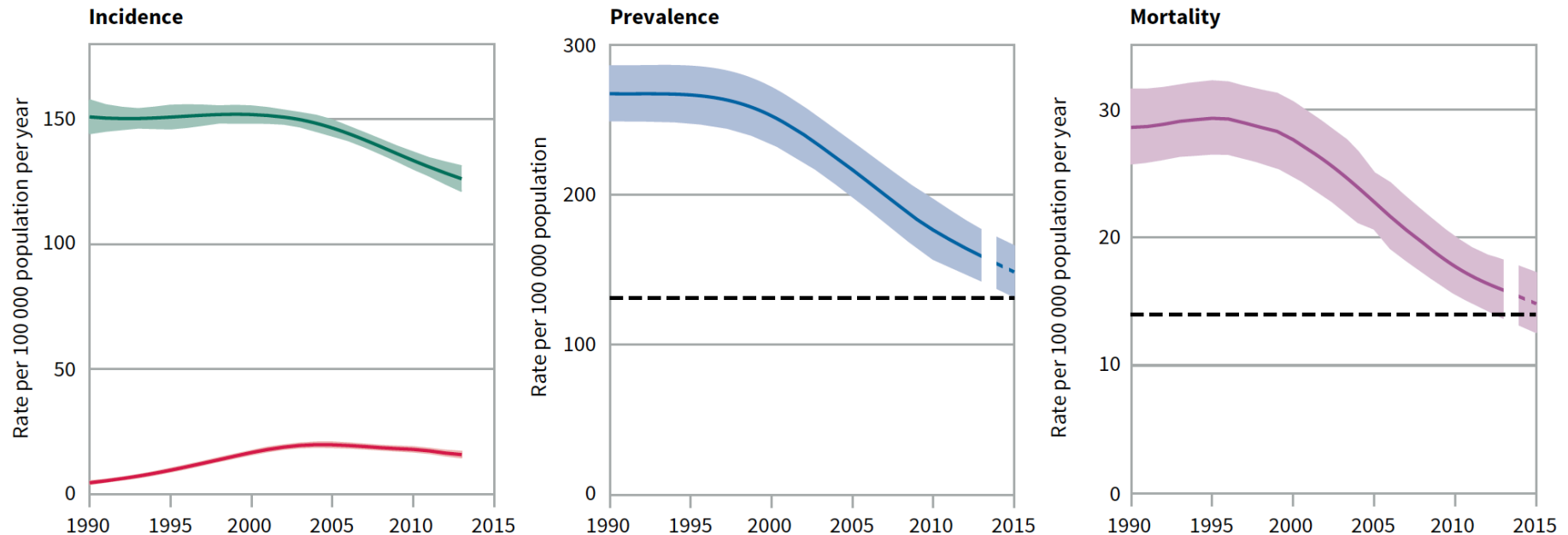
Global Epidemiology

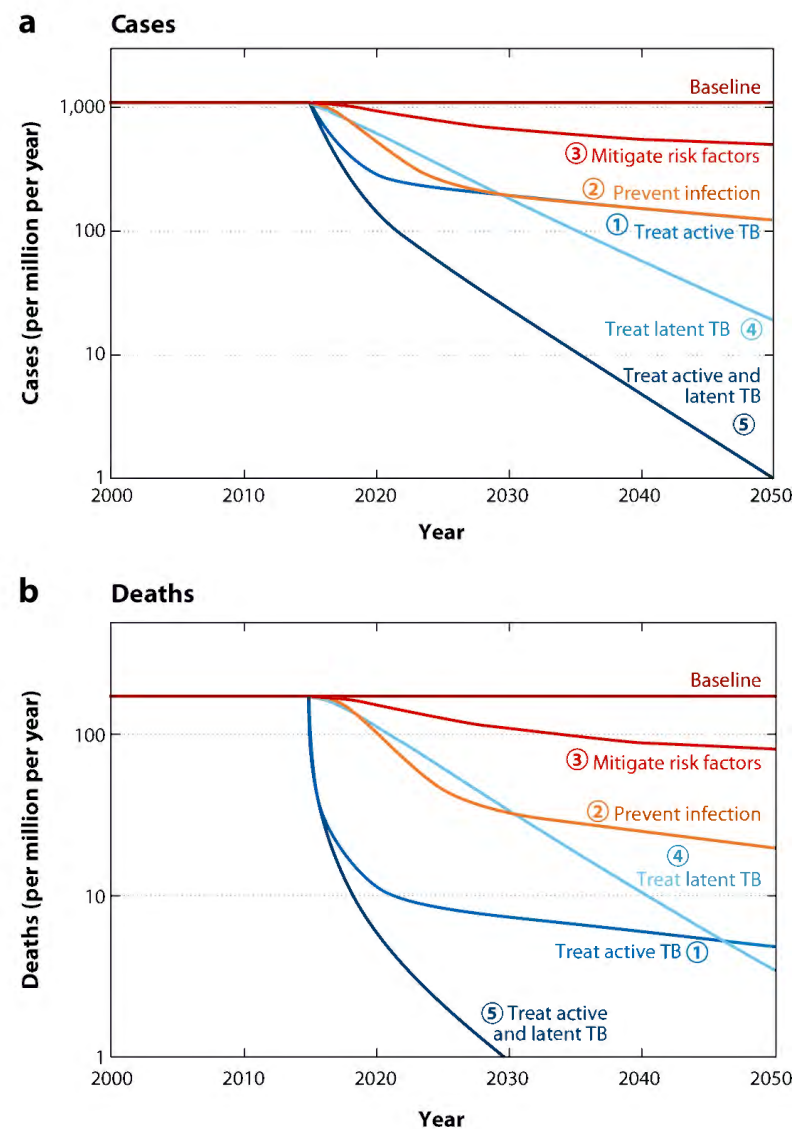
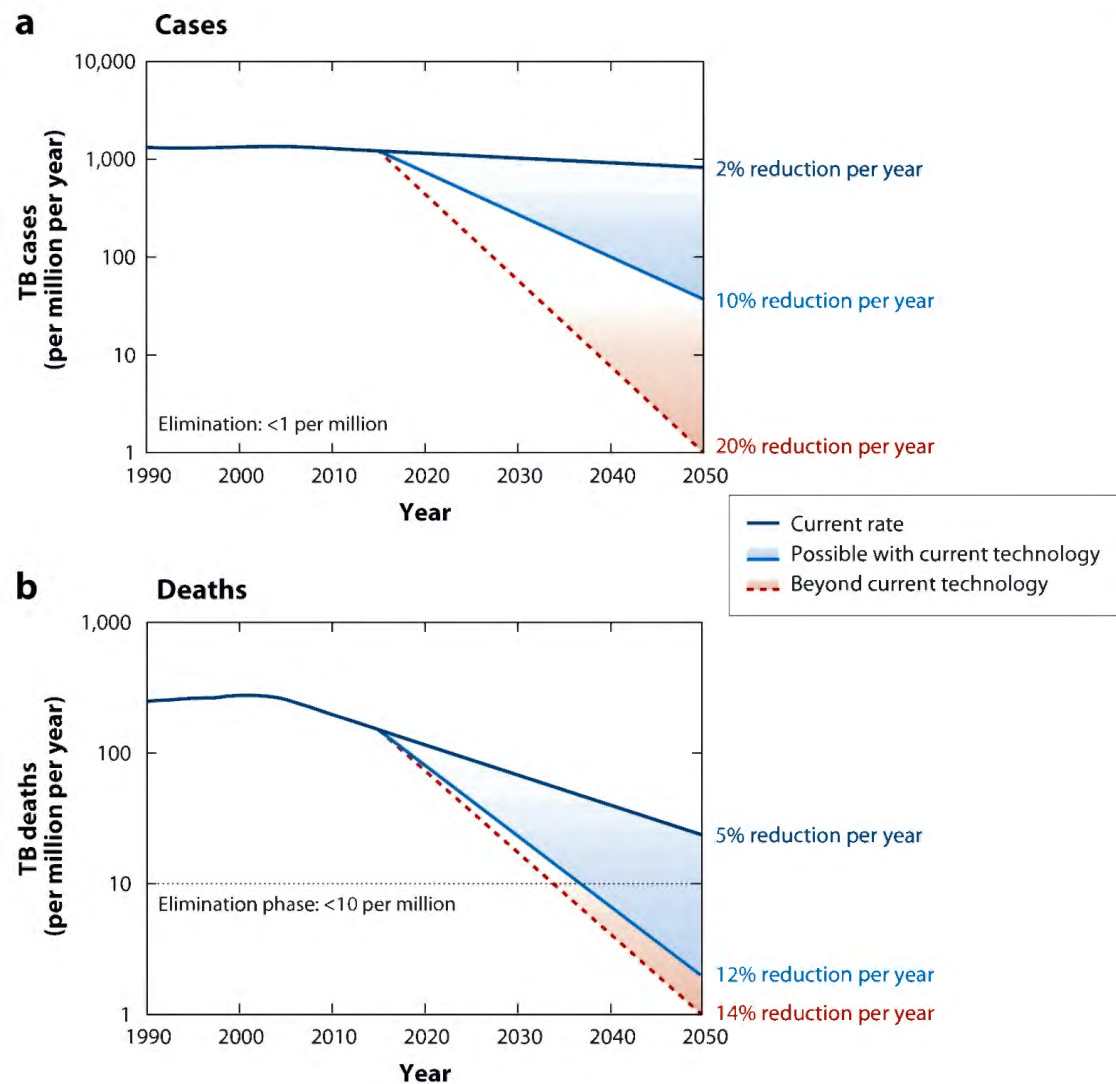
- Estimated 1/3 global population infected with TB
- 2013:
 - Estimated 9M new cases TB; 13% co-infected with HIV
 - 1.5M deaths from TB
 - Extreme global disparities in disease burden
 - India 24%, China 11% of global TB burden
 - Africa: 25% global burden; highest rate of infections and deaths per capita; 80% of HIV-TB co-infected cases
- Overall global TB incidence and mortality rates declining but MDR-TB rates increasing

Global Epidemiology

FIGURE 2.6

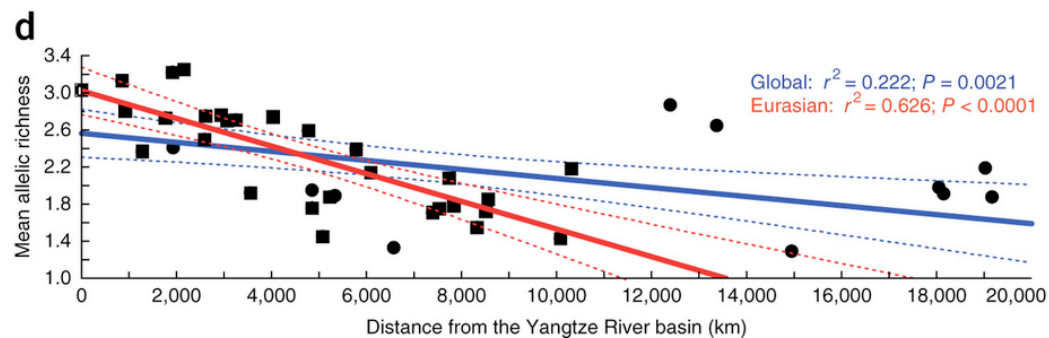
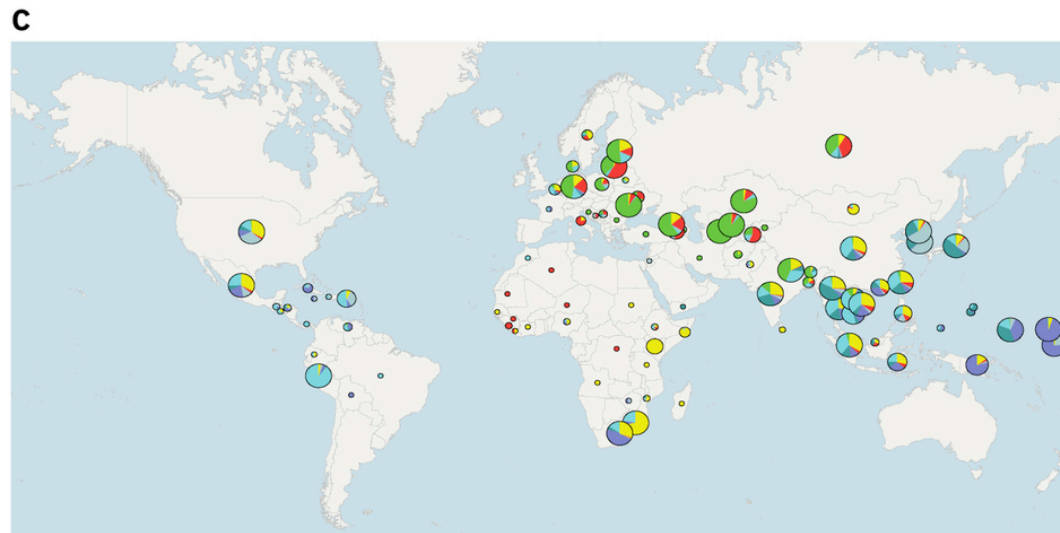
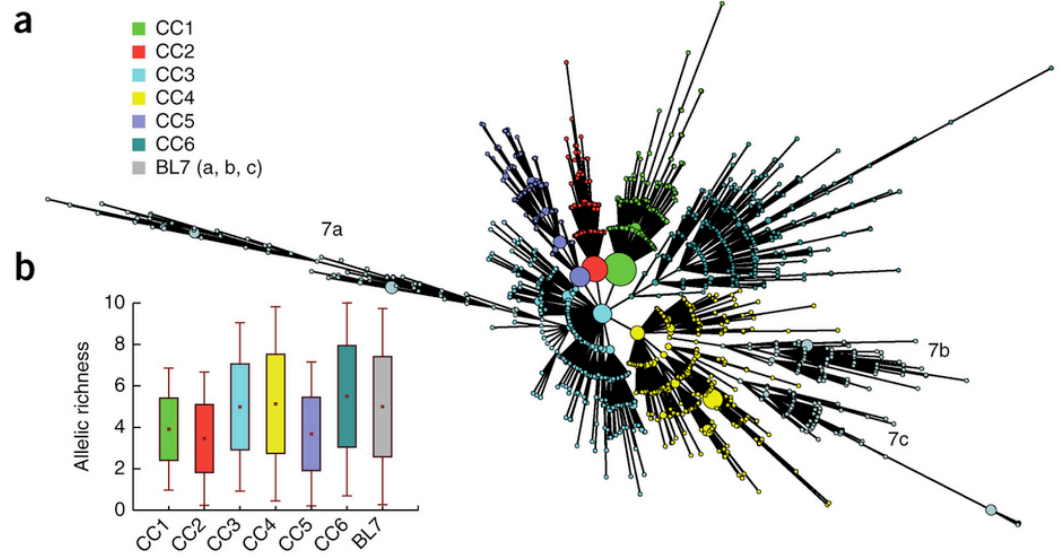
Global trends in estimated rates of TB incidence, prevalence and mortality. Left: Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: Trends in estimated TB prevalence and mortality rates 1990–2013 and forecast TB prevalence and mortality rates 2014–2015. The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.





AR Dye C, et al. 2013.
Annu. Rev. Public Health. 34:271–86





Global Epidemiology: Drug Resistance

- Multidrug-resistant (MDR) TB: TB resistant to both isoniazid and rifampin
- Overall treatment success rate 86% among new cases and 48% in MDR-TB cases
- Treatment requires use of less effective and more toxic drugs, extending treatment duration from 6 months to about 2 years
- 2013: Estimated 480,000 new MDR-TB cases with 210,000 deaths
- Rates of MDR-TB increasing
 - 3.5% new cases, 20.5% previously treated cases
 - India, China, Russia: >50% global MDR-TB burden
 - Estimated 9% of MDR-TB cases also XDR-TB
- Extensively drug-resistant (XDR) TB: MDR-TB also resistant to fluoroquinolones and 2nd-line injectable agents; very high rate of mortality and associated with late stage HIV infection

Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Lancet 2006; 368: 1575-80

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

	Group 1	Group 2	Group 3†	Total
Total tested	86	25	1428	1539
Culture-positive	45	22	475	542
MDR tuberculosis*	26	10	185	221 (14.4%)
XDR tuberculosis	17	6	30	53 (3.4%)

Data are number of patients. *Includes cases of XDR tuberculosis.

Table 1: Distribution of culture results and drug-resistance categories by group for all patients (n=1539) for whom sputum culture was done

	Number (%)
Tuberculosis characteristics (n=53)	
Pulmonary tuberculosis alone	40 (75%)
Pulmonary and extrapulmonary tuberculosis	13 (25%)
Sputum-smear positive	42 (79%)
Sputum-smear negative	11 (21%)
Previous tuberculosis treatment (n=47)	
No previous treatment	26 (55%)
Previous treatment: cure or completed treatment	14 (30%)
Treatment default or failure	7 (15%)
Previous admission in past 2 years (n=42)	
Admitted for any cause	28 (67%)
No previous admission	14 (33%)
HIV characteristics (n=44)	
HIV-infected	44 (100%)
On antiretroviral therapy	15 (34%)

Median CD4 63 range 9-283

Table 2: Characteristics of patients with XDR tuberculosis

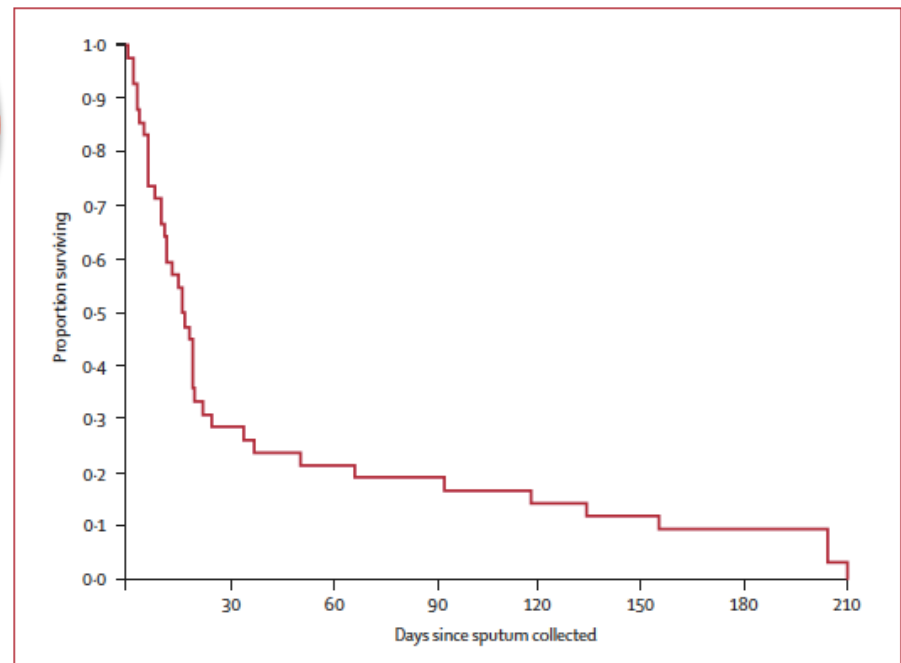


Figure: Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)

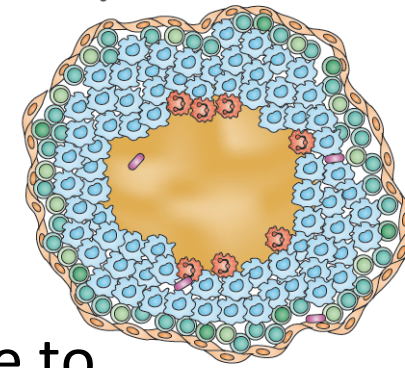
- 52/53 (98%) XDR TB patients died
- Among 42 with confirmed dates of death, median survival 16d (IQR 6-37)
- About 70% died within 30d of sputum culture collection

What we are watching—five top global infectious disease threats, 2012: a perspective from CDC's Global Disease Detection Operations Center

Kira A. Christian^{1*}, Kashef Ijaz¹, Scott F. Dowell¹, Catherine C. Chow¹, Rohit A. Chitale^{1†}, Joseph S. Bresee², Eric Mintz³, Mark A. Pallansch⁴, Steven Wassilak⁵, Eugene McCray⁶ and Ray R. Arthur¹

¹Division of Global Disease Detection and Emergency Response, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA; ²Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA; ³Division of Foodborne, Waterborne, and Enteric Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁴Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁵Global Immunization Division, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA; ⁶Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA

Disease outbreaks of international public health importance continue to occur regularly; detecting and tracking significant new public health threats in countries that cannot or might not report such events to the global health community is a challenge. The Centers for Disease Control and Prevention's (CDC) Global Disease Detection (GDD) Operations Center, established in early 2007, monitors infectious and non-infectious public health events to identify new or unexplained global public health threats and better position CDC to respond, if public health assistance is requested or required. At any one time, the GDD Operations Center actively monitors approximately 30–40 such public health threats; here we provide our perspective on five of the top global infectious disease threats that we were watching in 2012: (1) avian influenza A (H5N1), (2) cholera, (3) wild poliovirus, (4) enterovirus-71, and (5) extensively drug-resistant tuberculosis.

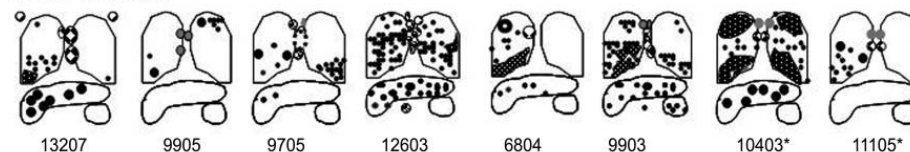


Pathogenesis

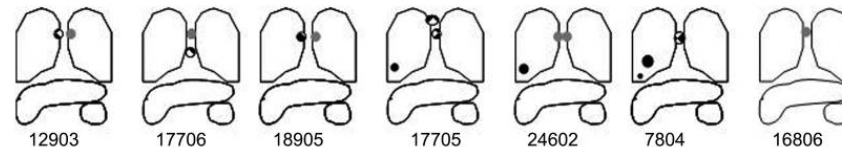
- Causes granulomatous inflammatory process due to macrophages, lymphocytes, and fibroblasts recruited to site of infection
 - Bacteria in granuloma may become dormant (latent)
 - Granuloma may have caseous necrosis in center
- Once latently infected, about 10% lifetime risk of developing active TB
 - About 5% over initial 2 years post infection
 - About 5% over remaining lifetime
- If co-infected with HIV, about 10% risk of activation each year
- Infection may spread via bloodstream (miliary); more common in young children and immunocompromised
- Infection naturally waxes and wanes



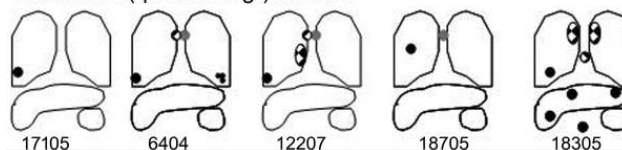
Active Disease



Latent Infection

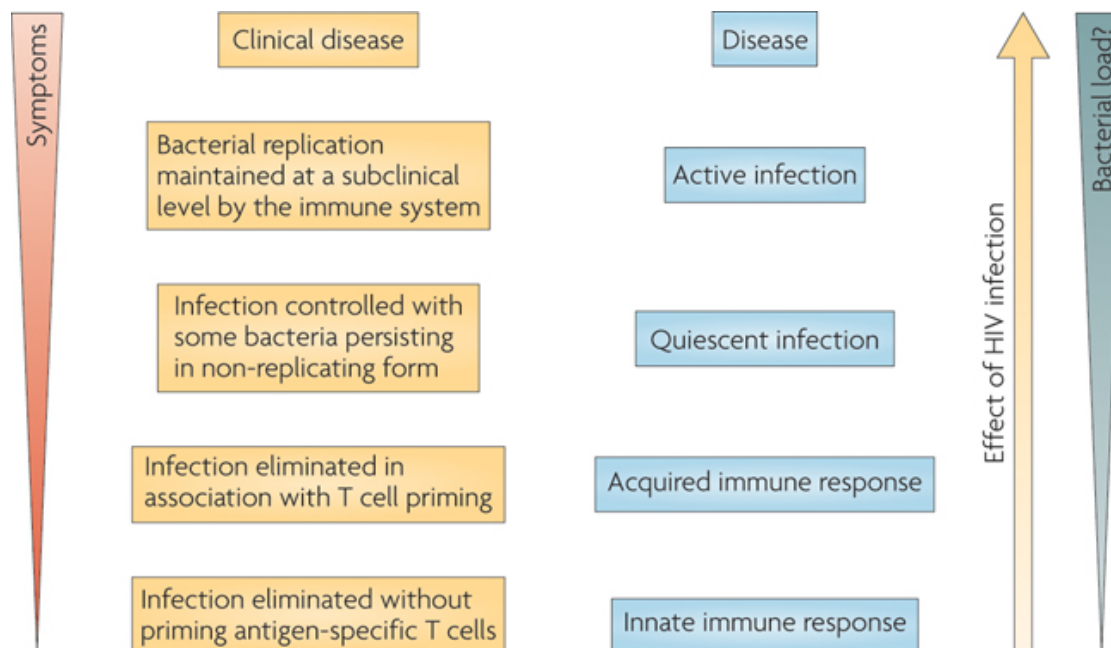


Subclinical ("percolating") disease



Infect Immun. 2009 Oct; 77(10): 4631–4642.

Nature Reviews Microbiology 2009 Dec 7, 845-855.



Diagnosis: Purified Protein Derivative (PPD)

- Mantoux tuberculin skin test
 - 5 tuberculin units (0.1 ml) of PPD tuberculin injected intradermally
 - Test is not specific for *M. tb*

Table 7. Criteria for tuberculin positivity, by risk group

Reaction ≥ 5 mm of induration	Reaction ≥ 10 mm of induration	Reaction ≥ 15 mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees [†] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of $\geq 10\%$ of ideal body weight, gastrectomy, and jejunioileal bypass	
	Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

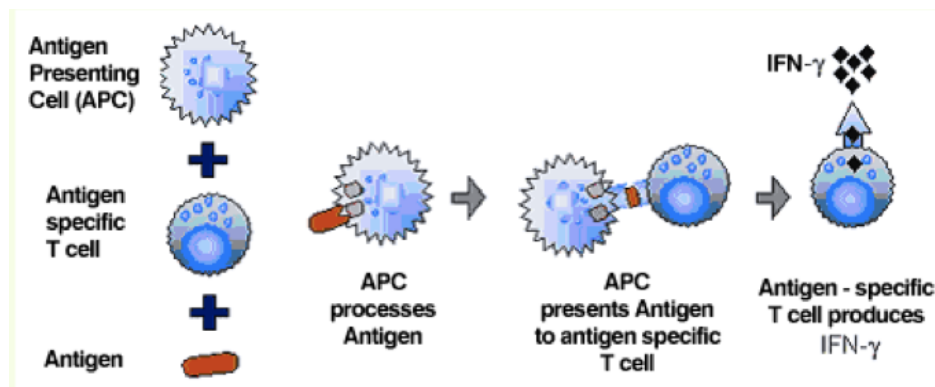
* Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

[†] For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥ 15 mm induration is considered positive.

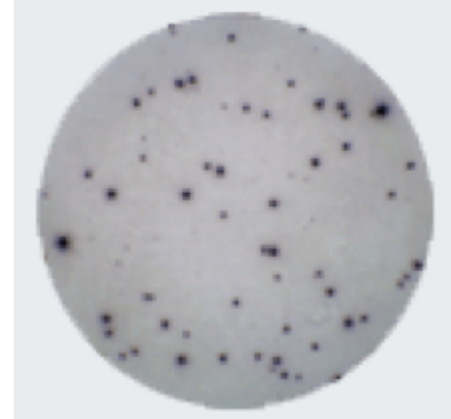
SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19–34.

Diagnosis: IGRA

- Interferon-gamma release assay (IGRA)
 - T-lymphocytes sensitized to specific antigens release IFN- γ when presented with antigen again
 - Measures IFN- γ response from T-lymphocytes to *M. tb* antigens (ESAT-6, CFP-10)
 - Assay not affected by BCG but *M. kansasii*, *M. szulgai*, *M. marinum* also contain ESAT-6/CFP-10
 - Cannot distinguish active from latent disease; cannot rule out active TB
 - Blood samples must be processed fresh (8-16 hrs)



Diagnosis: IGRA



- T-SPOT.TB
 - PBMCs isolated, added to 4 pre-coated wells (Nil, ESAT-6, CFP-10, mitogen), incubated O/N
 - Nil: negative control tube containing no Ag; measures baseline IFN- γ
 - Ag: ESAT-6, CFP-10
 - Mitogen: nonspecific IFN- γ stimulant; positive control
 - ELISpot assay used to detect number of cells secreting IFN- γ in each well
 - TB response = $\text{No. spots}_{\text{Ag}} - \text{No. spots}_{\text{Nil}}$

TABLE 3. Interpretation criteria for the T-SPOT.TB Test (T-Spot)

Interpretation	Nil*	TB Response†	Mitogen§
Positive¶	≤10 spots	≥8 spots	Any
Borderline**	≤10 spots	5, 6, or 7 spots	Any
Negative††	≤10 spots	≤4 spots	Any
Indeterminate**	>10 spots ≤10 spots	Any <5 spots	Any <20 spots

* The number of spots resulting from incubation of PBMCs in culture media without antigens.

† The greater number of spots resulting from stimulation of peripheral blood mononuclear cells (PBMCs) with two separate cocktails of peptides representing early secretory antigenic target-6 (ESAT-6) or culture filtrate protein-10 (CFP-10) minus Nil.

§ The number of spots resulting from stimulation of PBMCs with mitogen without adjustment for the number of spots resulting from incubation of PBMCs without antigens.

¶ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

†† Interpretation indicating that *M. tuberculosis* infection is not likely.

Diagnosis: IGRA

- QuantiFERON-TB Gold In-Tube (QFT-GIT) Assay
 - Blood collected in 3 heparinized tubes:
 - Nil: negative control tube containing no Ag; measures baseline IFN- γ
 - Ag: contains ESAT-6, CFP-10, TB7.7
 - Mitogen: nonspecific IFN- γ stimulant; positive control
 - Tubes incubated 16-24 hrs; IFN- γ levels measured
 - TB response = IFN- γ_{Ag} – IFN- γ_{Nil}

TABLE 2. Interpretation criteria for the QuantiFERON-TB Gold In-Tube Test (QFT-GIT)

Interpretation	Nil*	TB Response [†]	Mitogen Response [§]
Positive [¶]	≤8.0	≥0.35 IU/ml and ≥25% of Nil	Any
Negative**	≤8.0	<0.35 IU/ml or <25% of Nil	≥0.5
Indeterminate ^{††}	≤8.0	<0.35 IU/ml or <25% of Nil	<0.5
	>8.0	Any	Any

* The interferon gamma (IFN- γ) concentration in plasma from blood incubated without antigen.

[†] The IFN- γ concentration in plasma from blood stimulated with a single cocktail of peptides representing early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and part of TB 7.7 minus Nil.

[§] The IFN- γ concentration in plasma from blood stimulated with mitogen minus Nil.

[¶] Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating that *M. tuberculosis* infection is not likely.

^{††} Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

Latent TB Treatment

Table 10. Recommended drug regimens for treatment of latent tuberculosis (TB) infection in adults

Drug	Interval and duration	Comments	Rating* (Evidence) [†]	
			HIV-	HIV+
Isoniazid	Daily for 9 mo ^{‡,§}	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
	Twice weekly for 9 mo ^{‡,§}	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (III)
Isoniazid	Daily for 6 mo [‡]	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 mo [‡]	DOT must be used with twice-weekly dosing	B (III)	C (II)
Rifampin plus pyrazinamide	Daily for 2 mo	May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible TB	B (III)	A (I)
Rifampin plus isoniazid	Daily for 3 mo	For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide	B (III)	A (II)
	Twice weekly for 2–3 mo	DOT must be used with twice-weekly dosing	B (III)	C (II)
Rifampin	Daily for 4 mo	For persons who cannot tolerate pyrazinamide	B (III)	B (III)
		For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide		

* Strength of recommendation: A—preferred; B—acceptable alternative; C—offer when A and B cannot be given.

[†] Quality of evidence: I—randomized clinical trial data; II—data from clinical trials that are not randomized or were conducted in other populations; III—expert opinion.

[‡] Recommended regimen for children younger than 18 yr of age.

[§] Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 mo as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

[¶] Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see Table 8).

CDC MMWR Dec 9, 2011

- Weekly INH + rifapentine by DOT for 3 months considered equal alternative to INH x 9 months self administered
- For use in patients...
 - Age ≥ 12
 - High risk LTBI (close contact)
 - HIV if healthy, not on ARVS
- Not recommended for...
 - Age ≤ 2
 - HIV on ARVs
 - LTBI with contact to INH or RIF resistant index case

TB Treatment: Drug Sensitive

- Intensive Phase: isoniazid, rifampin, pyrazinamide, ethambutol (plus pyridoxine); (RIPE, HRZE)
 - Duration: 8 weeks (2 months); based on doses observed (DOT)
 - Ethambutol discontinued if drug susceptible
- Continuation Phase: isoniazid, rifampin
 - Duration: generally 4 months; based on doses observed (DOT)
 - Dosing can be daily, 3x/week, or 2x/week
 - Duration may be extended to 7 months if cavitary disease and/or still sputum culture positive at 2 months

Medication Side Effects: 1st Line

- **Isoniazid:** hepatotoxicity (esp. transaminases), rash, peripheral neuropathy, drug-induced lupus
- **Rifampin:** hepatotoxicity (esp. elevated bilirubin), rash, thrombocytopenia, orange-red discoloration of body fluids, renal failure; caution drug interactions
- **Pyrazinamide:** hepatotoxicity, elevated uric acid, gout
- **Ethambutol:** loss of visual acuity/color discrimination; peripheral neuropathy

The NEW ENGLAND JOURNAL of MEDICINE

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VOL. 363 NO. 11

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Xpert MTB/RIF

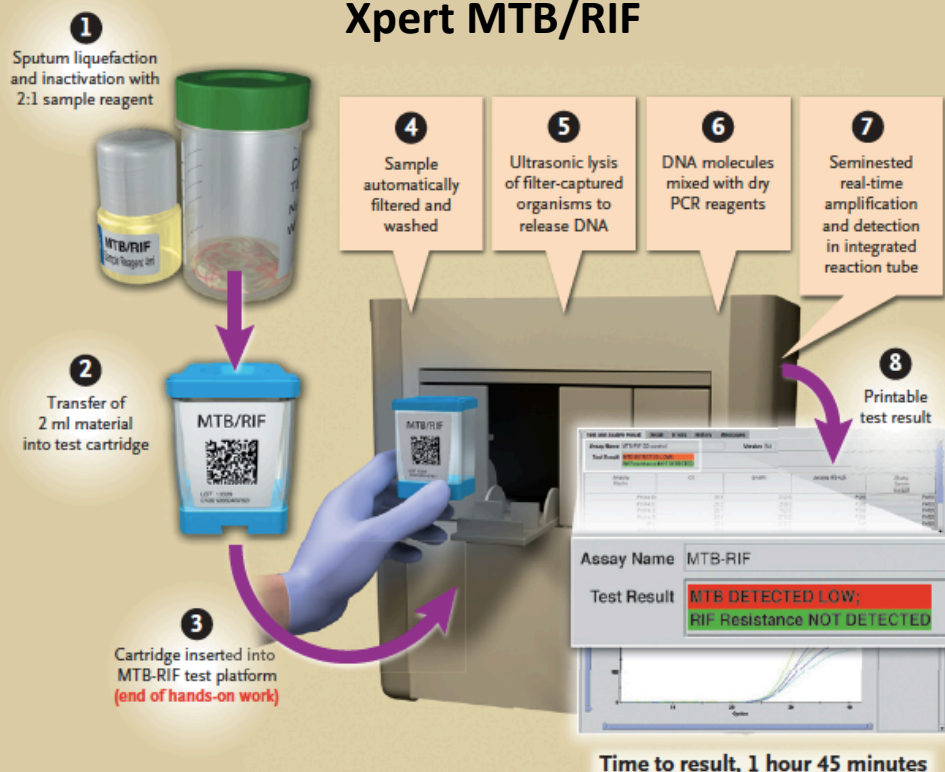


Table 2. Overall Sensitivity and Specificity of the MTB/RIF Test, According to the Number of Tests per Patient, as Compared with Three Smears and Four Cultures.*

Site and No. of Tests	Sensitivity			Specificity
	All Culture-Positive	Smear-Positive and Culture-Positive	Smear-Negative and Culture-Positive	No Tuberculosis
Site				
Lima, Peru				
Correct — no./total no. (%)	209/211 (99.1)	199/199 (100)	10/12 (83.3)	102/102 (100)
95% CI	96.6–99.7	98.1–100.0	55.2–95.3	96.4–100.0
Baku, Azerbaijan				
Correct — no./total no. (%)	144/149 (96.6)	80/80 (100.0)	64/69 (92.8)	68/70 (97.1)
95% CI	92.4–98.6	95.4–100.0	84.1–96.9	90.2–99.2
Cape Town, South Africa				
Correct — no./total no. (%)	142/148 (95.9)	95/96 (99.0)	47/52 (90.4)	186/189 (98.4)
95% CI	91.4–98.1	94.3–99.8	79.4–95.8	95.4–99.5
Durban, South Africa				
Correct — no./total no. (%)	43/45 (95.6)	30/30 (100.0)	13/15 (86.7)	213/219 (97.3)
95% CI	85.2–98.8	88.6–100.0	62.1–96.3	94.2–98.7
Mumbai, India				
Correct — no./total no. (%)	185/188 (98.4)	162/162 (100.0)	23/26 (88.5)	35/36 (97.2)
95% CI	95.4–99.5	99.7–100.0	71.0–96.0	85.8–99.5
No. of MTB/RIF tests				
3 Samples (2 pellet and 1 direct)				
Correct — no./total no. (%)	723/741 (97.6)	566/567 (99.8)	157/174 (90.2)	604/616 (98.1)
95% CI	96.2–98.5	99.0–100.0	84.9–93.8	96.6–98.9
2 Samples (1 pellet and 1 direct)				
Correct — no./total no. (%)†	1423/1482 (96.0)	1127/1134 (99.4)	296/348 (85.1)	1215/1232 (98.6)
95% CI	94.6–97.1	98.6–99.7	79.7–89.2	97.5–99.2
1 Sample (direct)				
Correct — no./total no. (%)	675/732 (92.2)	551/561 (98.2)	124/171 (72.5)	604/609 (99.2)
95% CI	90.0–93.9	96.8–99.0	65.4–78.7	98.1–99.6

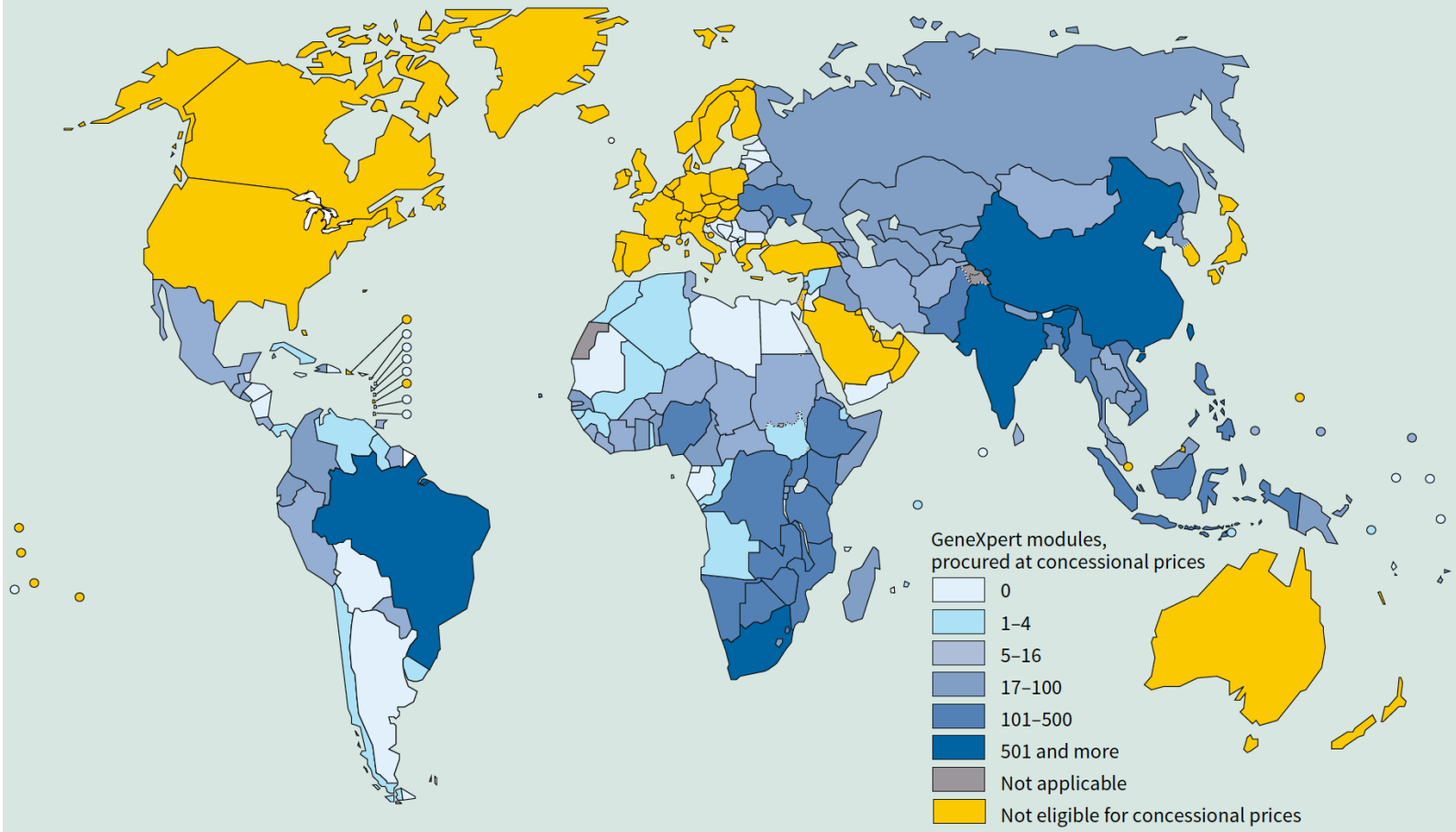
Figure 2. Assay Procedure for the MTB/RIF Test.

Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected; RIF resistance not detected." PCR denotes polymerase chain reaction.

GeneXpert Global Scale-up

FIGURE B6.1.1 3269 machines procured by 108/145 countries eligible for concessional prices

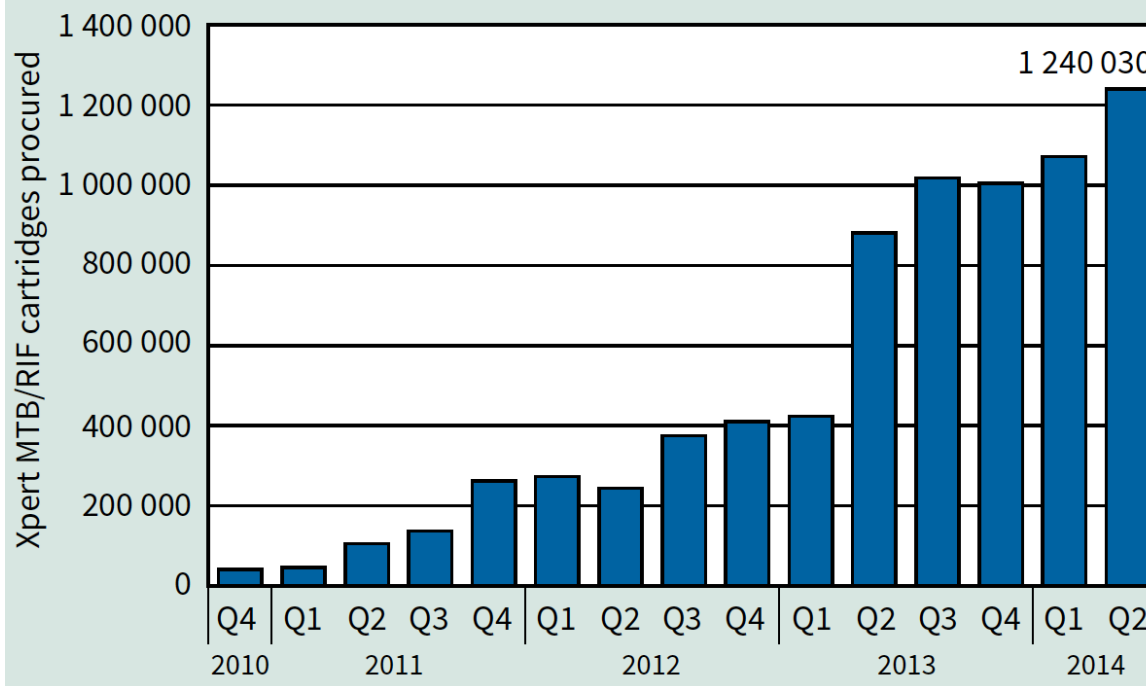
Global capacity for Xpert MTB/RIF testing, by June 2014



GeneXpert Global Scale-up

FIGURE B6.1.2

Quarterly number of Xpert MTB/RIF cartridges procured at concessional prices, October 2010 – end June 2014



7.5 million cartridges procured by 108/145 countries eligible for concessional prices

MDR-TB Treatment

MDR-TB TREATMENT DRUGS AND RELATED TOXICITIES

GROUP	DRUG	SEVERE OR COMMON TOXICITIES	COMMENTS
Group 1 First-line Agents – Generally well tolerated	Pyrazinamide (Pza)*	<ul style="list-style-type: none"> - Hepatotoxicity (<1% with current dosing) - Hyperuricemia and gout - Anorexia, vomiting 	<ul style="list-style-type: none"> - WHO guidelines recommend routine use despite 50% - 70% MDR resistance rates in some regions; reliable DST
	Ethambutol (Emb)*	<ul style="list-style-type: none"> - Central or peripheral retrobulbar neuritis in <1% cases 	<ul style="list-style-type: none"> - No longer recommended for routine use in MDR-TB treatment because benefit not been shown
Group 2 Injectable Agents	Aminoglycosides: • Kanamycin (Km)* • Amikacin (Amk)	<ul style="list-style-type: none"> - Irreversible ototoxicity (6-18%) and in some cases may develop months after discontinuation 	<ul style="list-style-type: none"> - Parenteral administration only - Km is preferred due to cost, but if resistance probable, Cm should be used
	Cyclic polypeptide: • Capreomycin (Cm)	<ul style="list-style-type: none"> - Nephrotoxicity - risk increased in elderly, renal impairment, and use with other nephrotoxic agents 	<ul style="list-style-type: none"> - Cross-resistance patterns are variable and complex - local drug choice often made on basis of cost and availability
Group 3 Fluoroquinolones	Moxifloxacin (Mfx)* Levofloxacin (Lfx) Ofloxacin (Ofx)	<ul style="list-style-type: none"> - Generally well tolerated - GI disturbance - nausea, vomiting, diarrhea - Neurologic disturbance – insomnia, restlessness; In less than 0.5%: agitation, confusion, depression - Dose-related QT prolongation common, so avoid use with long Q-T syndrome and caution with other drugs prolonging Q-T interval 	<ul style="list-style-type: none"> - Optimal Mfx and Lfx doses not definitively established - Ofx substantially less potent - Use of ciprofloxacin is not recommended
Group 4 Bacteriostatic Second-line Agents (in order of preference)	Ethionamide (Eto) Prothionamide (Pto)*	<ul style="list-style-type: none"> - Frequent GI intolerance – anorexia, nausea, vomiting, metallic taste - Neurotoxicity: seizures, psychosis, depression - Peripheral and optic neuropathy - Hepatotoxicity (2%) - Hypothyroidism 	<ul style="list-style-type: none"> - Active against katG mutants, but not inhA and other relevant mutations - No substantial difference in toxicity between analogues - Divided doses (BID or TID) and/or initial dose ramping over 1-2 weeks may improve tolerance - Less effective with history of previous MDR- TB treatment - Pyridoxine should be added
	Cycloserine (Cs) Terizidone (Trd)	<ul style="list-style-type: none"> - Common CNS effects: mood changes, confusion, psychosis, paranoia, aggression, vertigo, tremor 	<ul style="list-style-type: none"> - Terizidone may have less CNS toxicity, but not proven - Dose reduction common

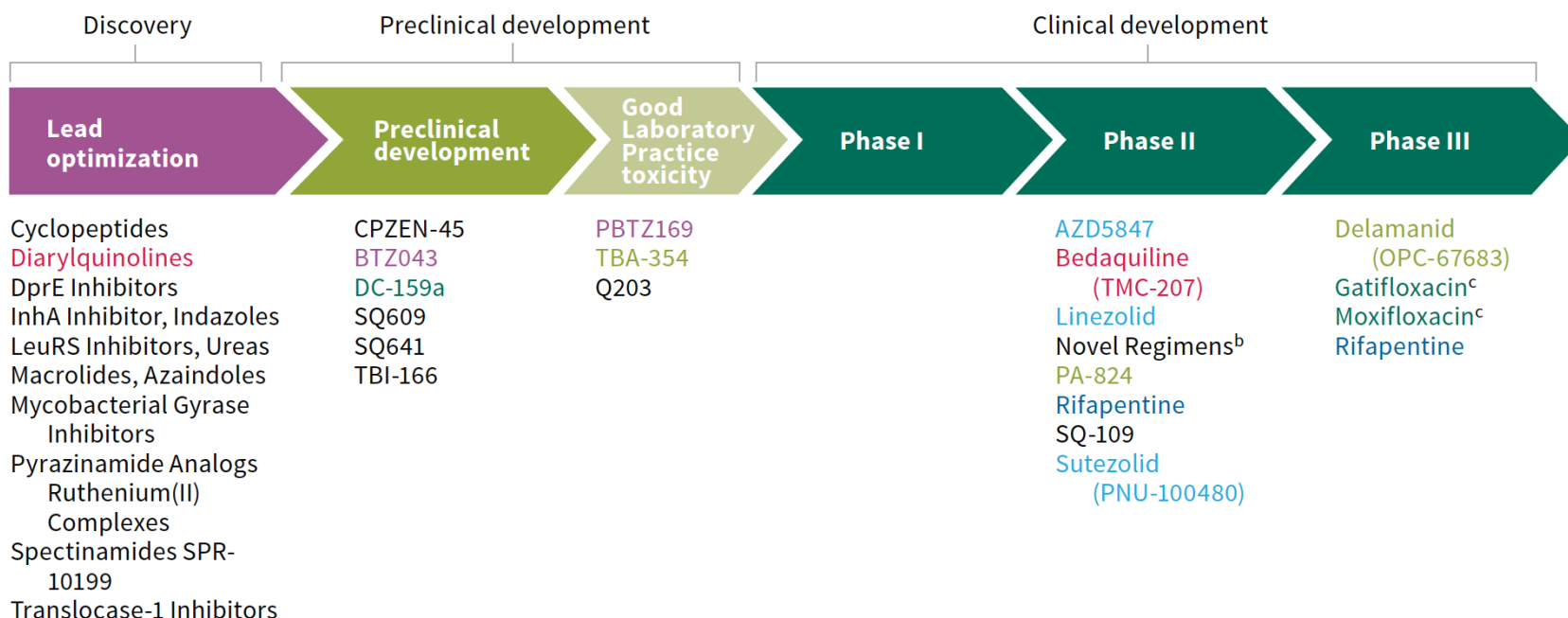
MDR-TB Treatment

GROUP	DRUG	SEVERE OR COMMON TOXICITIES	COMMENT
			- High-dose pyridoxine (150-300 mg/day) should be added
	Para-aminosalicylic acid (Pas)	- Frequent GI intolerance: anorexia, nausea, vomiting, diarrhea - Hepatotoxicity approx. 0.5% - Hypothyroidism	- Weak static activity only, but helps to prevent emergence of resistance - Granular form and divided dosing are usually better tolerated
Group 5 Agents with unclear role in MDR-TB Treatment (use only as needed for regimen to have at least 4 high-probability active second-line drugs)	High dose isoniazid (High-dose Inh)*	- Hepatotoxicity – Risk increases with age (2% with age > 50y), liver disease, other hepatotoxic drugs; - Rash (2%); - Neurotoxicity risk is increased with higher dose, CNS – seizure, hallucinations, mental changes, depression; - Peripheral neuropathy, rarely optic neuritis	- Unlikely to have activity against katG mutant strains, but may be active against most inhA mutant strains - Pyridoxine should be added
	Clofazimine (Cfz)*	- Red to brown skin discoloration with intensity related to dose and duration; - Dose-related GI disturbance: nausea, vomiting, And cramps - Q-T prolongation has been observed, but not carefully studied	- While role in treatment is not yet clear, has substantial activity in animal models - Optimal dosing not established - High barrier to resistance development - Extremely high/prolonged tissue and macrophage concentrations vs. serum
	Linezolid (Lzd)	- Nausea, diarrhea, and headache - With long-term use: Peripheral neuropathy, thrombocytopenia, infrequently optic neuropathy - Myelosuppression common; - Rarely, lactic acidosis, pancreatitis	- Has substantial sterilizing activity - High barrier to resistance - Relatively high cost - Dose reduction (600 daily to 300 mg daily) often required to allow continuation
	Amoxicillin/Clavulanate (Amx/Clv)	- Generally well tolerated - GI disturbance related to dose of Clv - Rarely, hypersensitivity/anaphylaxis	- Role in MDR-TB therapy not defined, but some case reports indicate possible benefit - Imp/Cln intravenous only
	Imipenam/Cilastatin (Imp/Cln)		- Emb may be synergistic and increases activity, even at sub-inhibitory concentrations
	Clarithromycin (Clr)	- Generally well tolerated; - GI disturbance common – nausea, cramping, diarrhea, abnormal taste - Q-T interval prolongation	- Potent inhibitor of CYP3A - Activity is low, but may synergize with Pza and activity may be significantly enhanced by Emb, if susceptible - High lung tissue levels

TB Drug Pipeline

FIGURE 9.2

The development pipeline for new TB drugs, August 2014^a



Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

^a Details for projects listed can be found at <http://www.newtbdrugs.org/pipeline.php> and ongoing projects without a lead compound series identified can be viewed at <http://www.newtbdrugs.org/pipeline-discovery.php>

^b Combination regimens: NC-001-(J-M-Pa-Z), Phase IIa, NCT01215851; NC-002-(M-Pa-Z), Phase IIb, NCT01498419; NC-003-(C-J-Pa-Z), Phase IIa, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), Phase IIb, NCT01785186

^c These trials have been completed and results published. See chapter text for further details.

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OCTOBER 23, 2014

VOL. 371 NO. 17

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Hatherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Mungofa, M.P.H., Nasir A. Shah, M.B., B.S., Simukai Zizhou, M.B., Ch.B., Lloyd Magweta, M.B., Ch.B., James Shepherd, Ph.D., Sambayawo Nyirenda, M.D., Janneke H. van Dijk, Ph.D., Heather E. Clouting, M.Sc., David Coleman, M.Sc., Anna L.E. Bateson, Ph.D., Timothy D. McHugh, Ph.D., Philip D. Butcher, Ph.D., and Denny A. Mitchison, F.R.C.P., for the RIFAQUIN Trial Team*

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*

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News > Global development

Drug companies join forces to combat deadliest tropical diseases

Bill Gates gets pharmaceutical giants to promise drug giveaways and unprecedented pledge to share research on new antidotes

Participants at today's CEO Roundtable event at the Royal College of Physicians include:

Dr. Margaret Chan, Director-General, World Health Organization

Bill Gates, Co-Chair, Bill & Melinda Gates Foundation

Dr. Jörg Reinhardt, Chairman of the Board of Management, Bayer HealthCare AG

Lamberto Andreotti, Chief Executive Officer, Bristol-Myers Squibb

Haruo Naito, President and CEO, Eisai

Sir Andrew Witty, Chief Executive Officer, GlaxoSmithKline

William Weldon, Chief Executive Officer, Johnson & Johnson

Kenneth Frazier, Chairman of the Board, President and Chief Executive Officer, MSD

Dr. Stefan Oschmann, Executive Board member, Merck KGaA

Joseph Jimenez, Chief Executive Officer, Novartis

Christopher A. Viehbacher, Chief Executive Officer, Sanofi

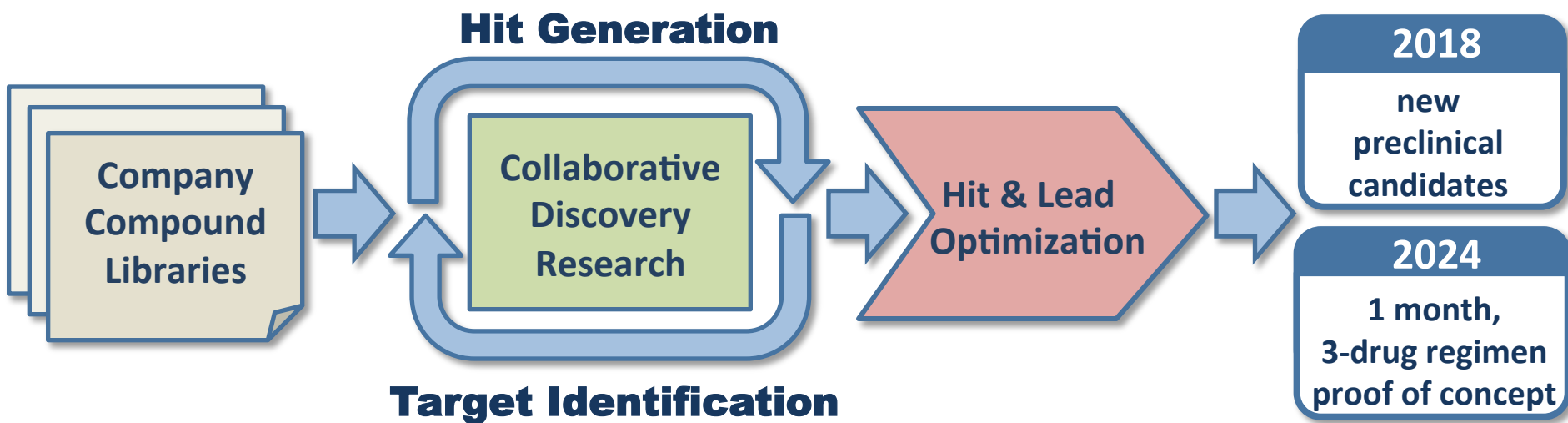
Paul Carter, Senior Vice-President, Gilead

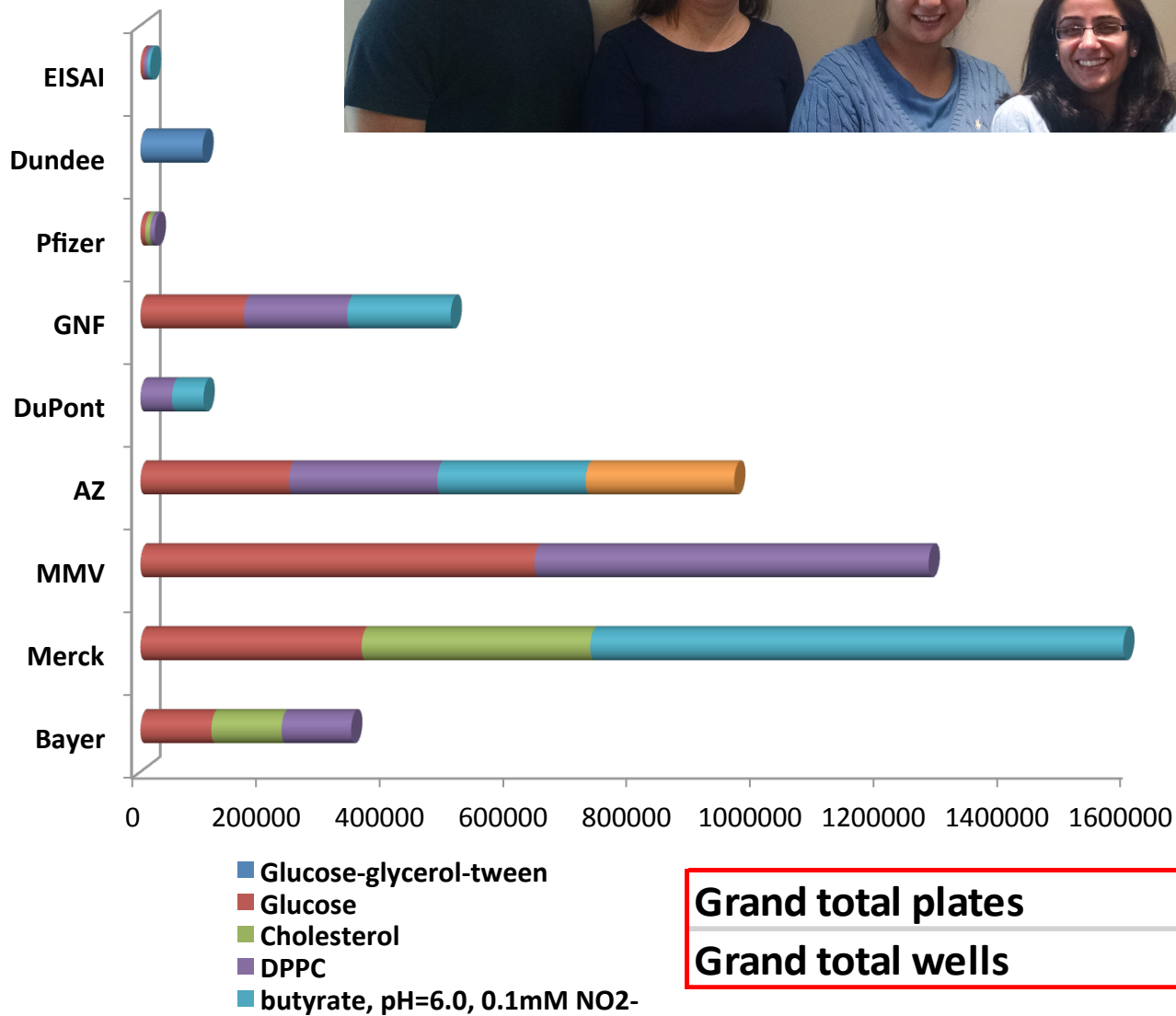
What is the TB Drug Accelerator?

The TBDA is a groundbreaking partnership between eight pharmaceutical companies, seven research institutions, and a product development partnership that seeks to develop a new TB drug regimen through collaboration in early-stage drug discovery research.



How the TBDA Works: Bringing Compounds from Library to Development





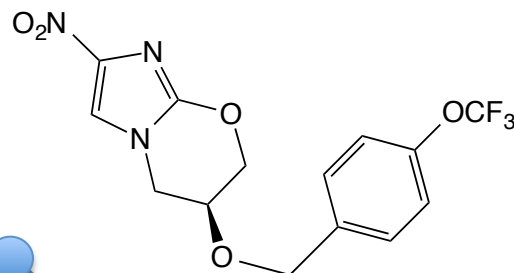
Grand total plates

15623

Grand total wells

5587744

HTS Hit



Request for analogs

Request for profiling

600 related structures
from 7 companies

Pre-TBDA: 5 FTE/ 5 years

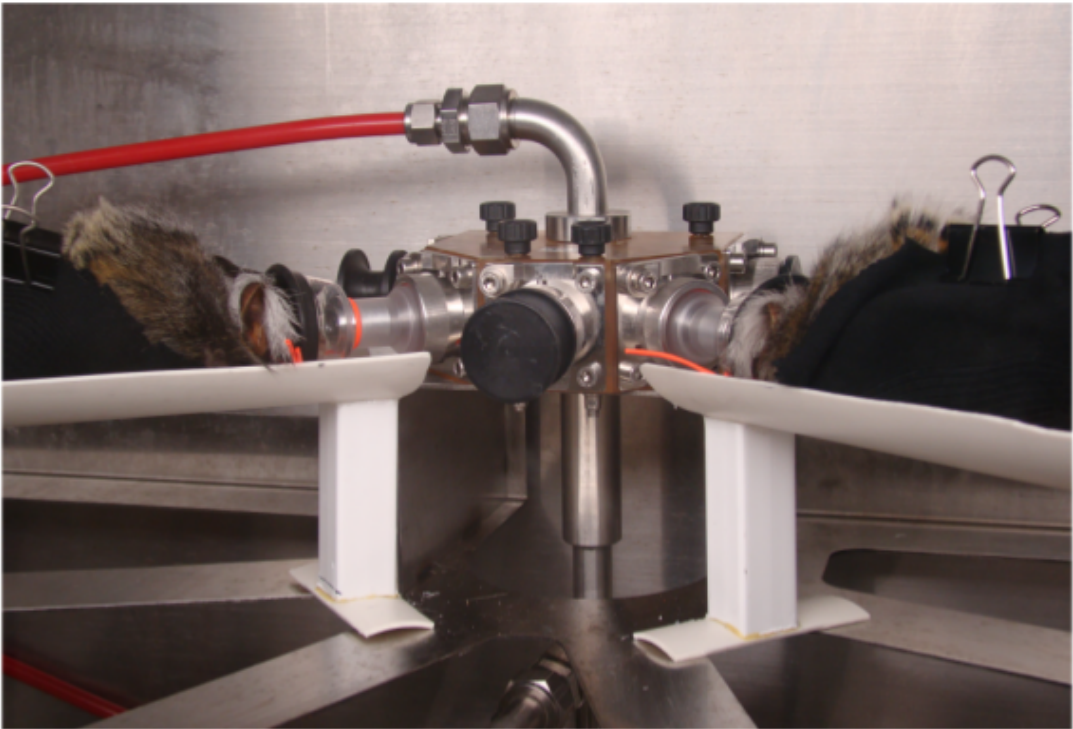
TBDA: < 6mo

Kinetic/Thermodynamic solubility (GSK)
Microsomal Stability (Abbvie)
Hepatic Clearance (Abbvie)
Cytochrome P-450 Inh/Sub (Abbvie)
Plasma Protein Binding (GSK)
POPK (AstraZeneca)
AMES mutagenicity testing (GSK)
hERG Activity (Abbvie)
In silico toxicity flags (multiple companies)
Promiscuous target profile (several companies)

Currently have 3200 hit compounds across 150 distinct chemical series.

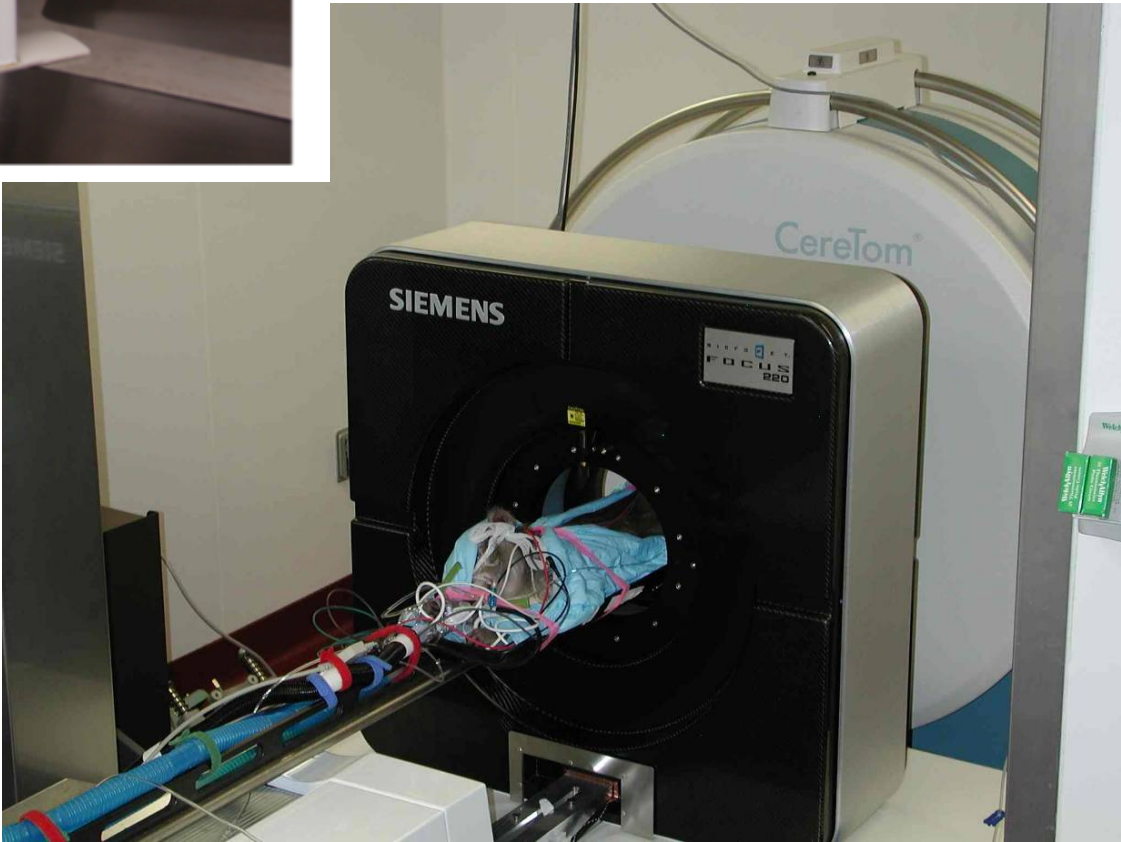
Our findings raise questions about progression decisions throughout the development pathway for tuberculosis drugs. Data from studies in mice predicted that the inclusion of moxifloxacin would result in a reduction of 1 to 2 months in the treatment duration, as compared with standard therapy.^{12,13} In our study of such treatment shortening, the moxifloxacin-containing regimens did not work adequately, suggesting that the murine model may have overpredicted the sterilizing potency of moxifloxacin in this regimen.





Common marmoset
Callithrix jacchus

Adult weight: 250-350g
Twinning rate: 80%
Cmpd Rqrmnt: 3g



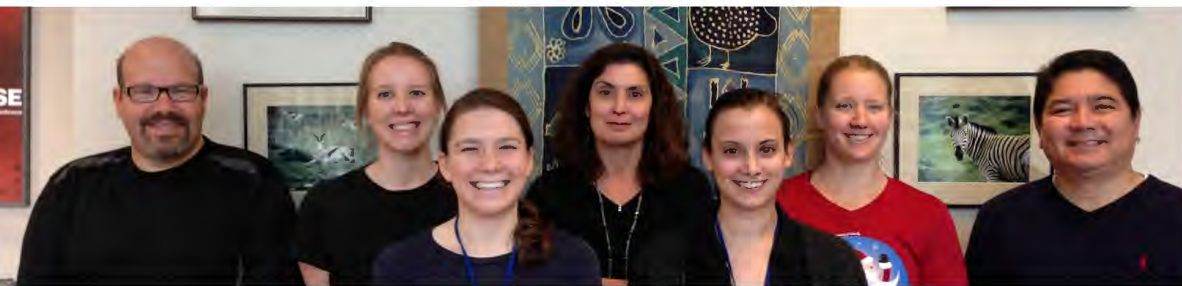
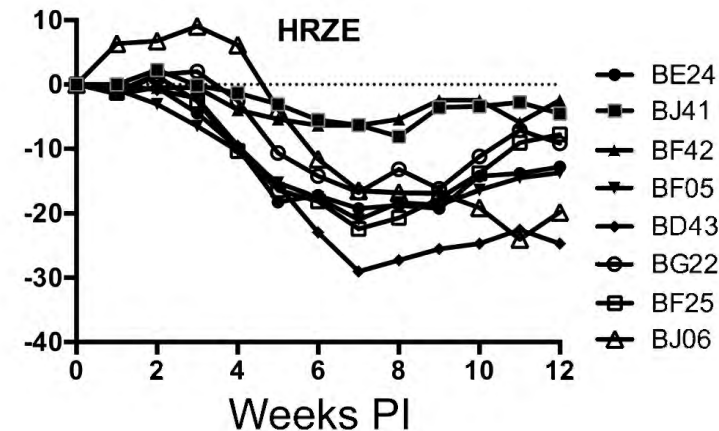
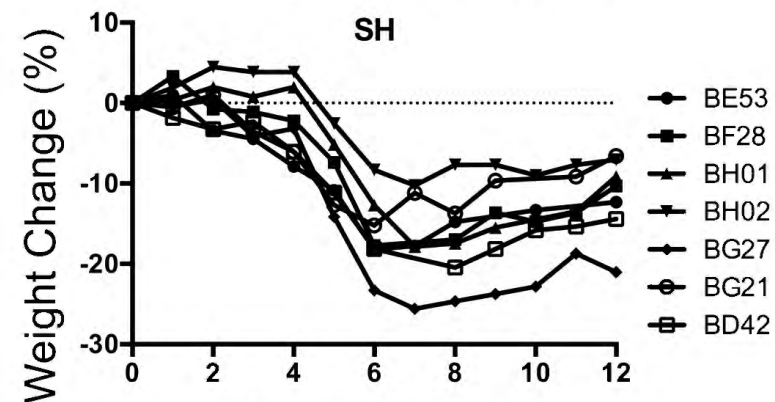
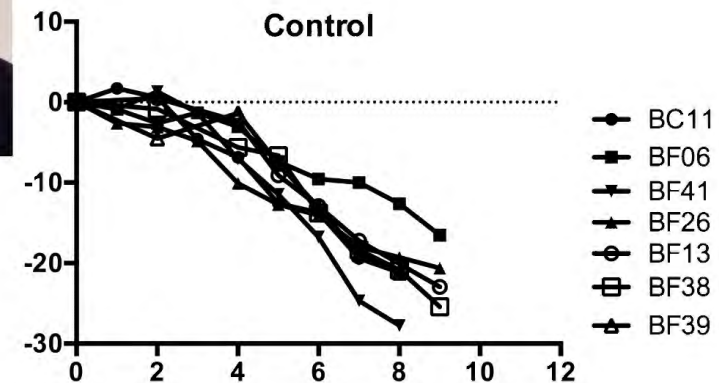
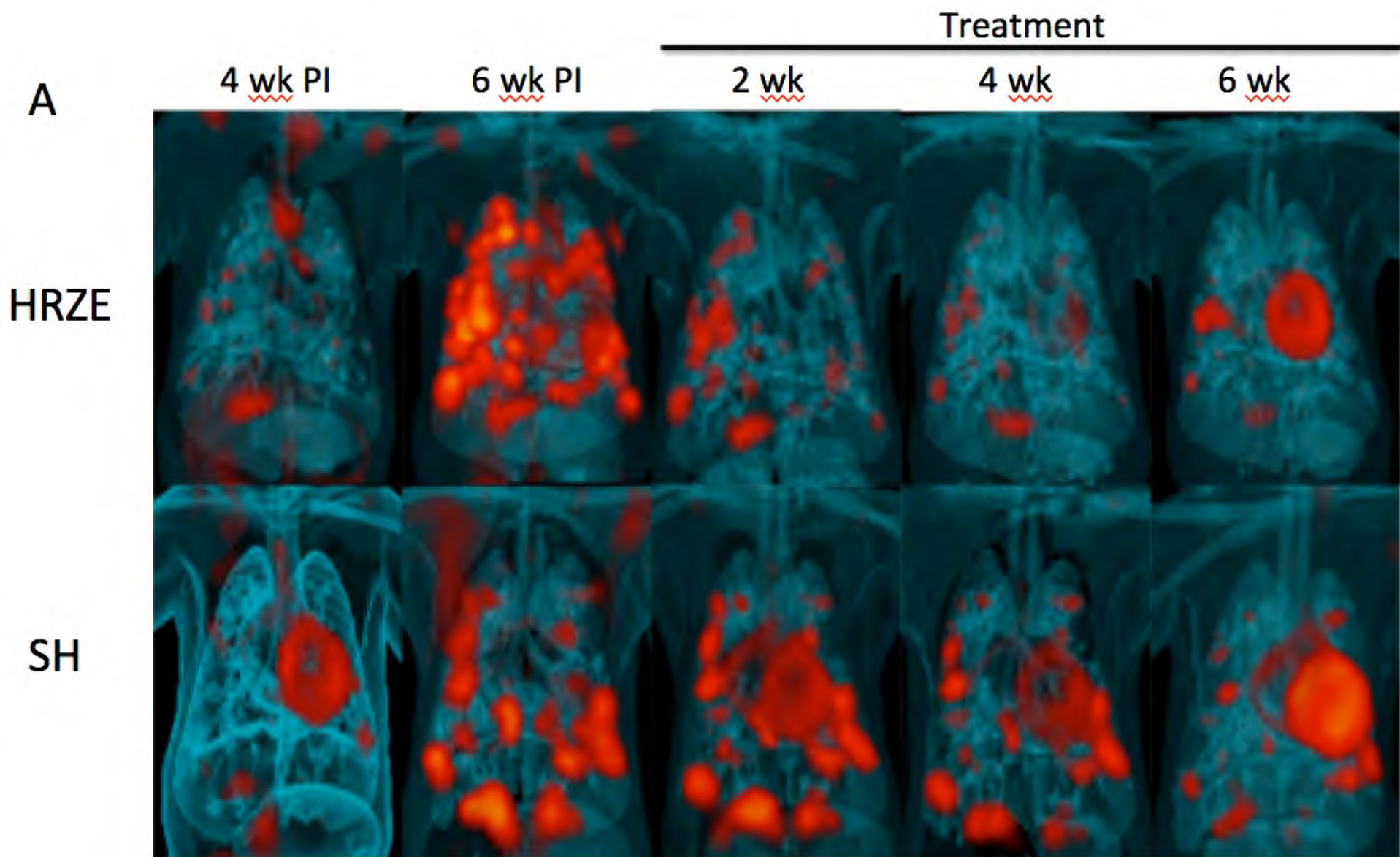


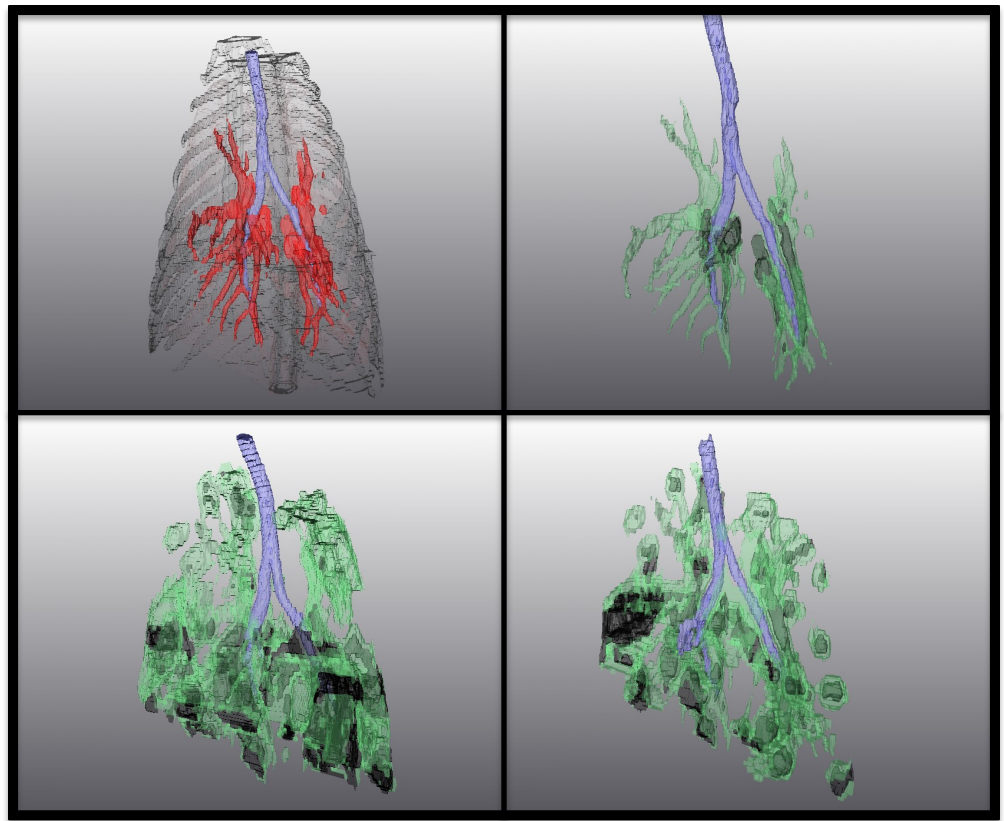
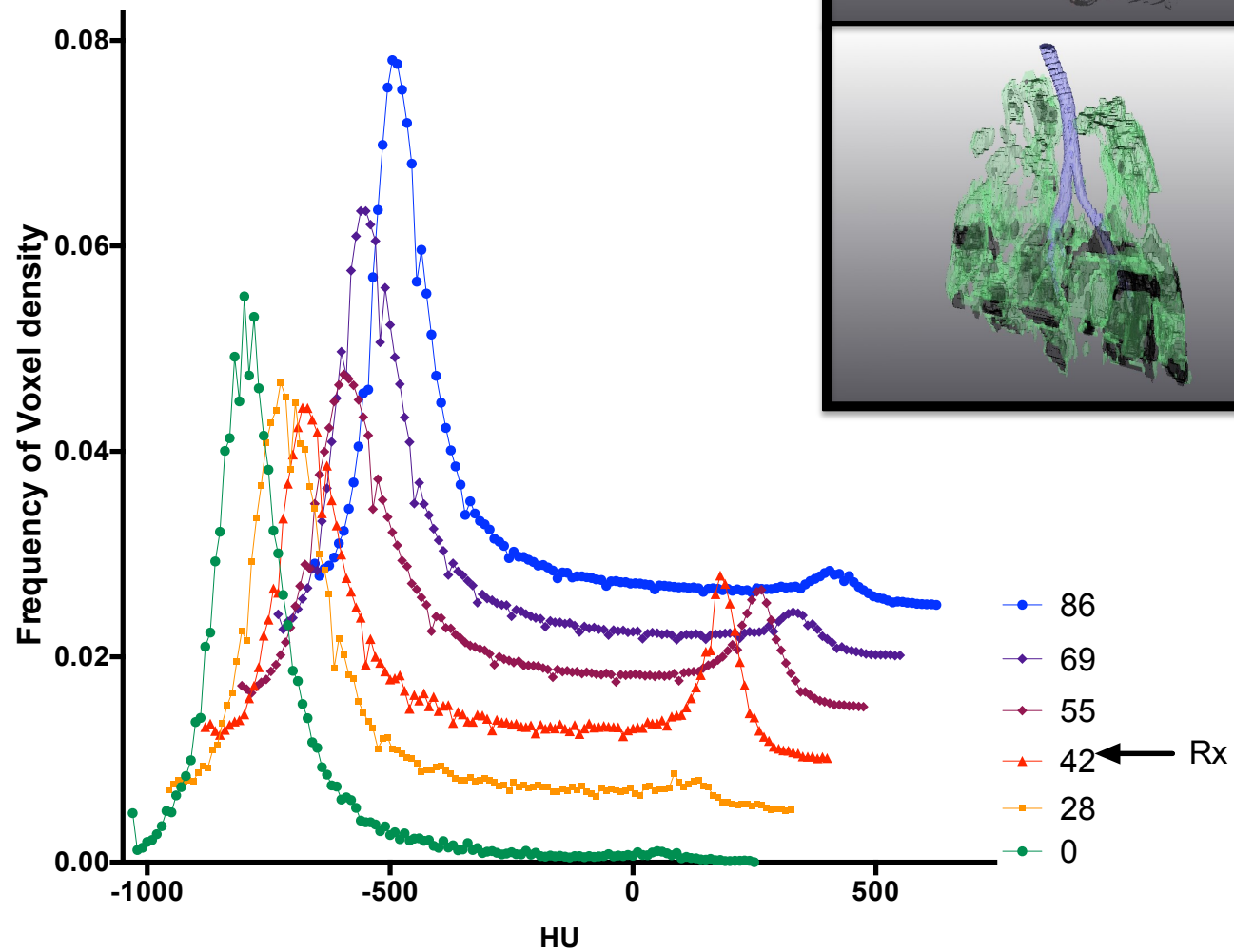
Table 1. Pharmacokinetic parameters of first line anti-TB drugs in Marmosets in comparison with published data from humans.

Drug	Dose (mg/kg)	Marmoset		Human			
		C_{max} mean ug/mL (range)	AUC ₍₁₋₂₄₎ mean (range)	Dose mg (mg/kg)	C_{max} mean ug/mL (95% CI)	AUC ₍₁₋₂₄₎ mean (ug*mL/hr) (95% CI)	
INH	30	5.0 (0.8-11)	11 (6-20)	300 (5)		53.0 (32-68)	1
RIF	15	17 (10-21)	191 (122-254)	450 (7.5)	9.6 (8.4-11)	50.6 (43-60)	2
EMB	75	3.9 (2.4-5.2)	13.4 (12-14)	750 (12.5)	2.0 (1.6-2.4)	13.5 (12-15)	2
PZA	125	34 (31-36)	153 (118-180)	1500 (25)	47 (44-50)	486 (422-519)	2
SM ^a	20	81 (60-95)	157 (157-200)	1000 (16.7)	43 (2.9-85) ^a	267(175-343) ^a	3

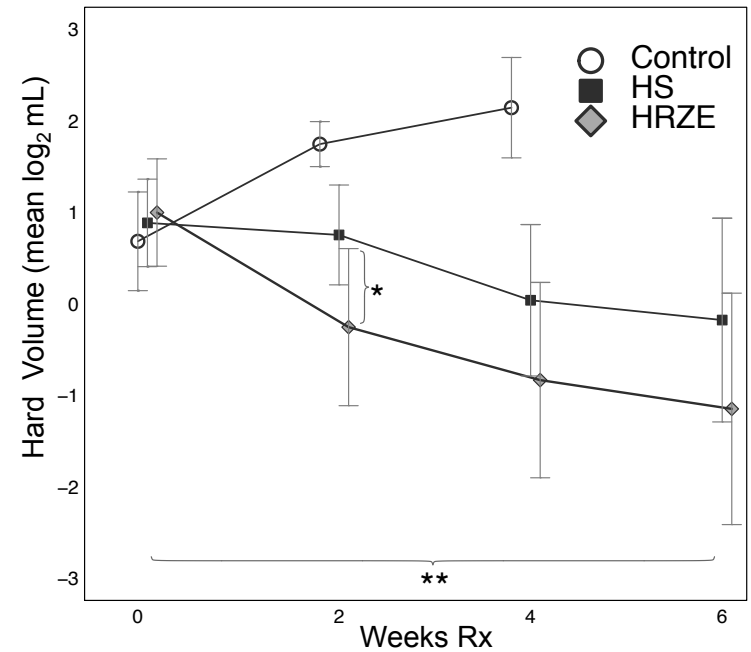
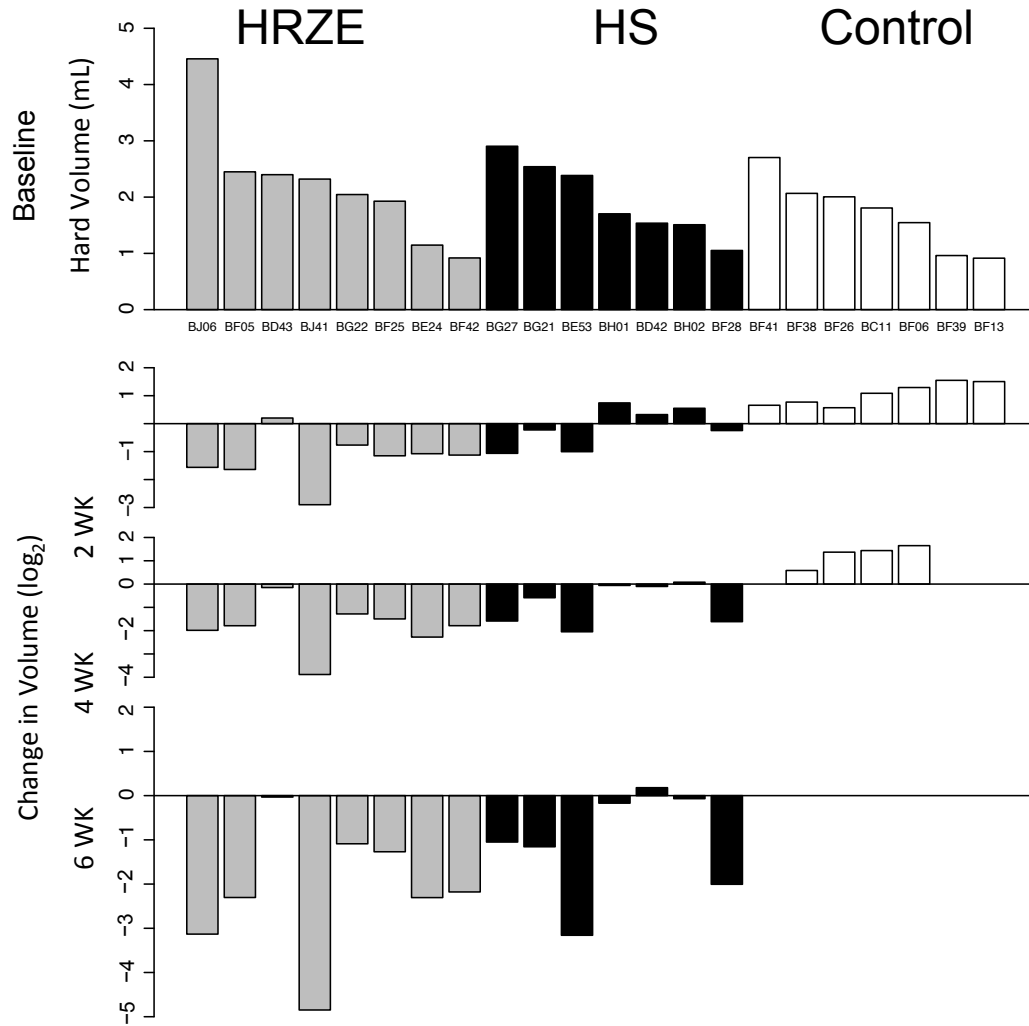
(1)Weiner et al., AJRCCM 167:1341-1347 (2003), (2)Ruslami et al., AAC, 10.1128/aac.00447-09; (3) Zhu et al., *Pharmacotherapy*, 2001, 21:9; ^adata are median and (range)







CT Changes in marmosets can distinguish optimal and suboptimal regimens




* Regimen Difference 2 Wk $p < 0.02$
** Regimens over time $p = 0.035$

Science Translational Medicine

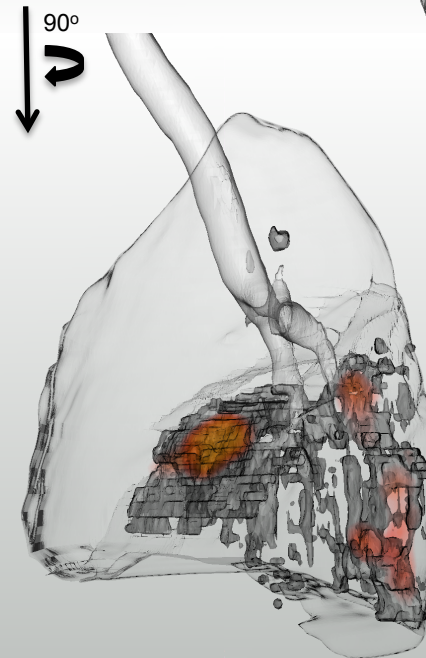
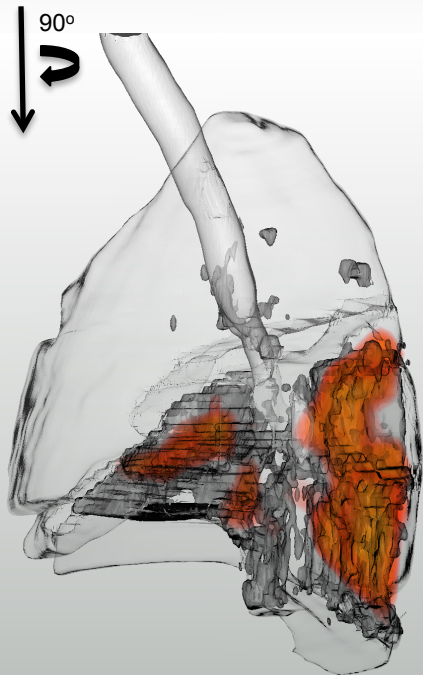
3 December 2014

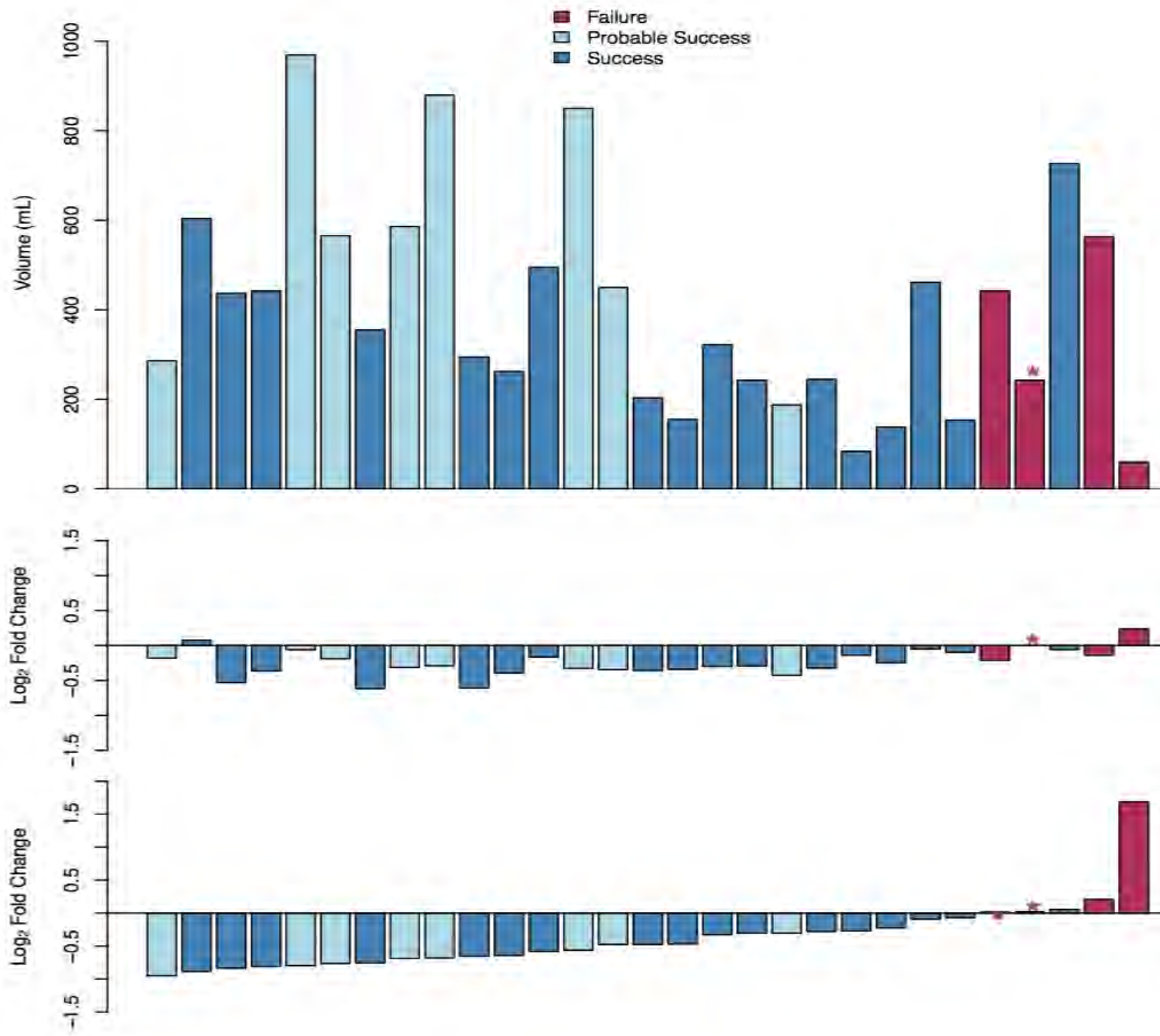


 AAAS

Study Entry

Day 56





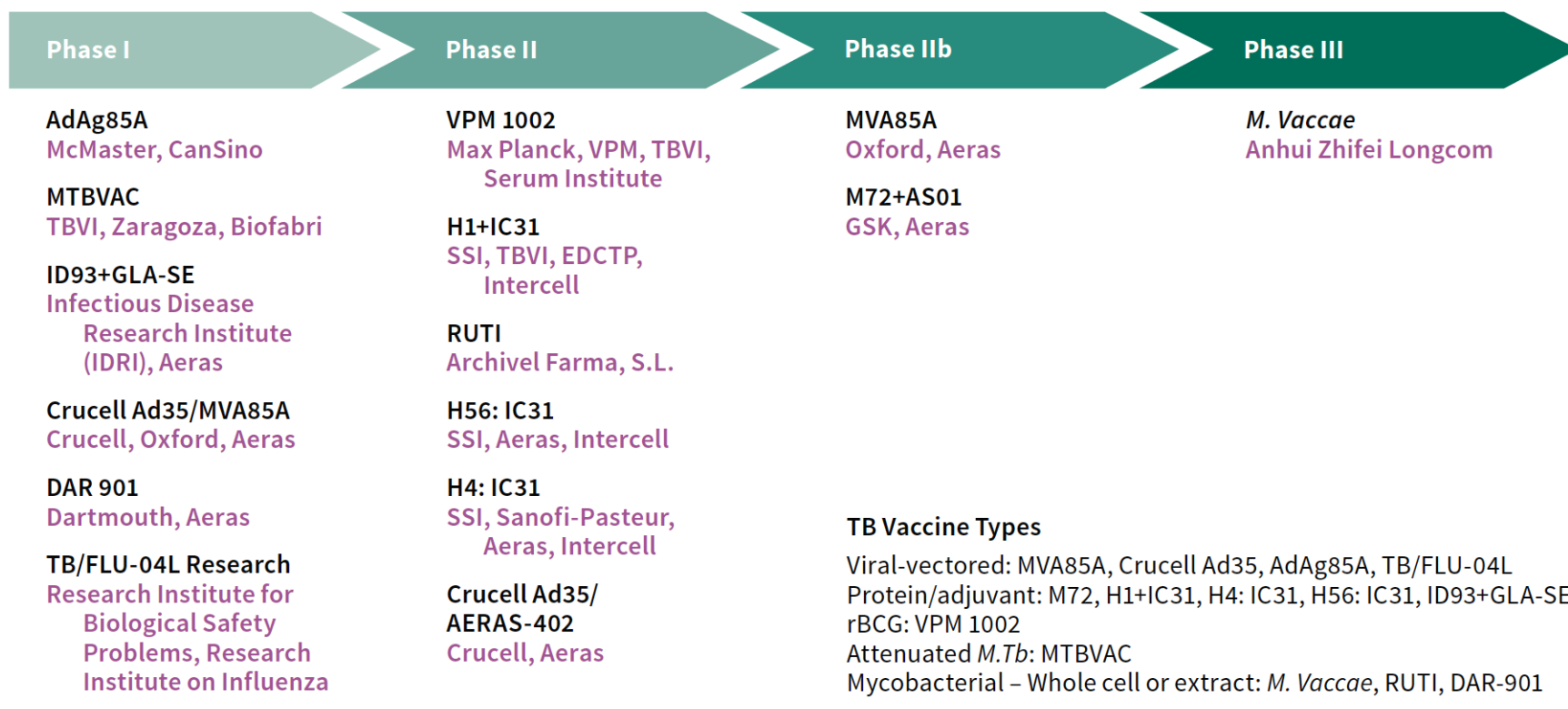
TB Vaccine: BCG

- Bacille Calmette-Guérin:
 - TB vaccine initially developed in 1921; based on attenuated *Mycobacterium bovis*
 - Overall protective effect and duration variable to none, particularly for pulmonary TB
 - Protective against disseminated TB (meningitis, miliary TB) in children
 - Cross-reacts with PPD TB skin test
- Current vaccines in clinical trials: either boost or replace BCG

TB Vaccines

FIGURE 9.3

The development pipeline for new TB vaccines, August 2014



Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team
www.thelancet.com Vol 381 March 23, 2013 *Lancet* 2013; 381: 1021–28

- Designed to boost BCG efficacy
- Double-blind, randomized, placebo-controlled trial from 7/2009-5/2011
- 2797 infants previously received BCG enrolled in Cape Town, SA

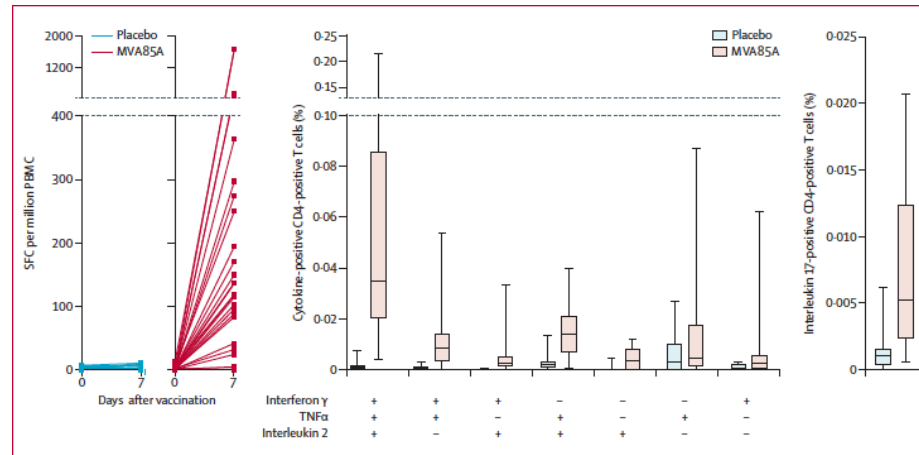


Figure 2: Vaccine immunogenicity
(A) Frequencies of Ag85A-specific T cells measured by interferon-γ enzyme-linked immunosorbent spot assay in infants in study group 2 (27 infants in the MVA85A group and 27 infants in the placebo group) before administration of placebo or MVA85A (day 0) and 7 days after vaccination. (B) Frequencies of cytokine-expressing Ag85A-specific Th1 (CD4-positive T cells expressing IFN-γ, TNFα, or Interleukin 2) and (C) frequencies of Ag85A-specific Th17 (CD4-positive T cells expressing Interleukin 17) cells, measured by whole blood intracellular cytokine staining 28 days after administration of placebo or MVA85A to infants in study group four (17 infants in the MVA85A group and 19 infants in the placebo group). SFC=spot-forming cells. PBM C=peripheral blood mononuclear cell.

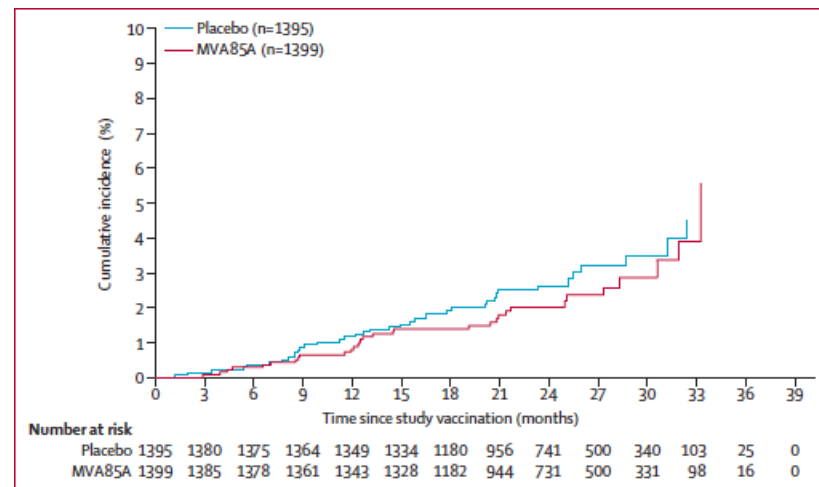


Figure 3: Cumulative incidence of diagnosis of tuberculosis endpoint 1

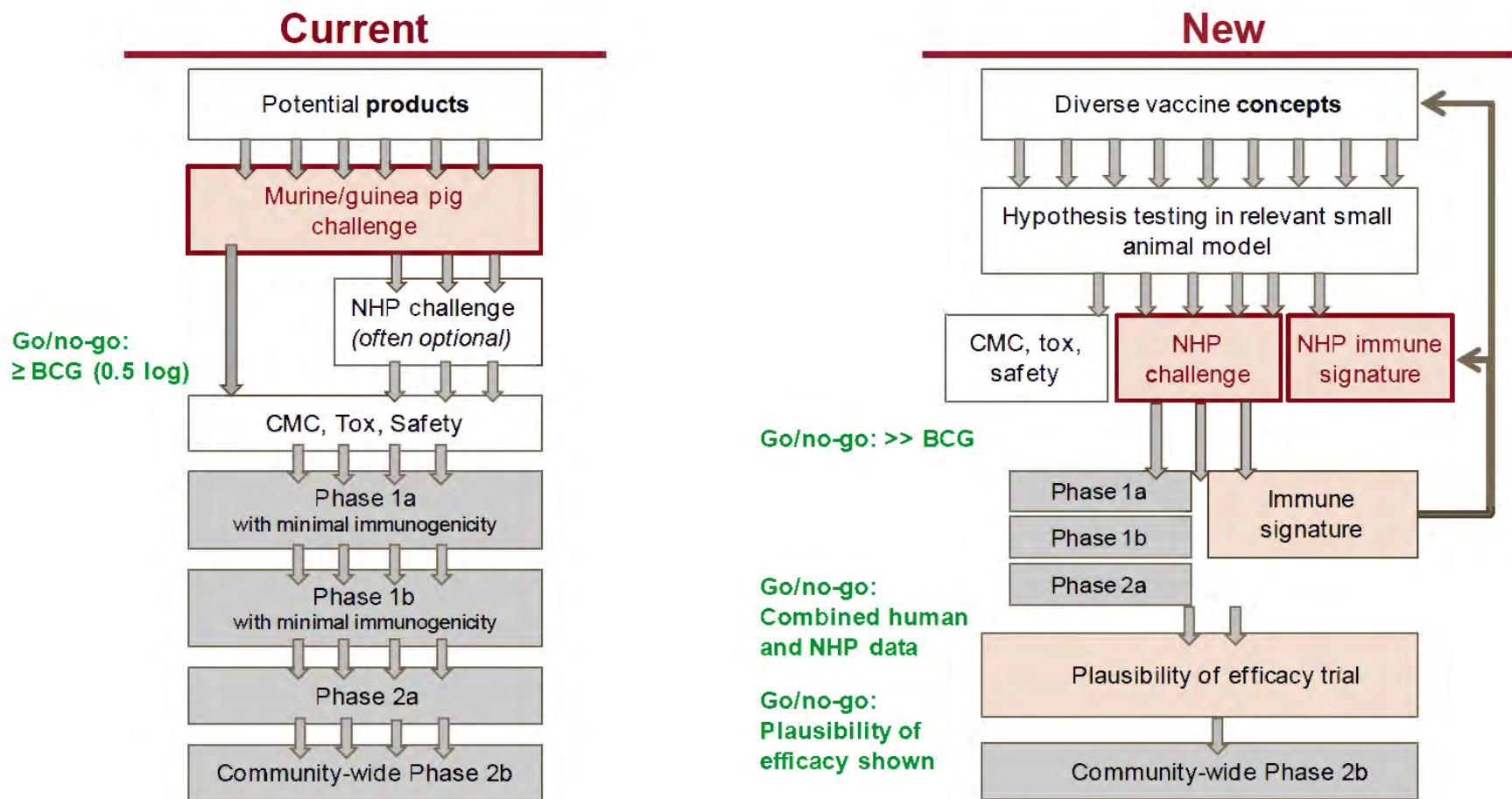


FIGURE 2. NEW PARADIGM FOR VACCINE CONCEPT SELECTION/PRODUCT DEVELOPMENT

Conclusions

- Despite small numbers of cases in the US, TB remains a significant cause of global public health morbidity and mortality
- Although TB rates in the US and globally have declined (except for rates of MDR-TB) due to effective drugs developed during the 20th century, we are not on target to achieve the MDG goal of eradication by 2050
- Infection is a spectrum from immune clearance of disease to latent, subclinical, and active disease; current diagnostic methods cannot differentiate between these states
- Diagnostic methods include PPD, IGRA, and GeneXpert
- Treatment recommendations for latent and active disease have not changed significantly since 2000
- Active research is ongoing to develop improved animal models for TB, better diagnostic methods, new drugs and drug regimens to shorten treatment duration, and more protective vaccines

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